A Dissertation on

PREVALENCE OF PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600 032

With partial fulfillment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH – I

COIMBATORE MEDICAL COLLEGE
COIMBATORE
APRIL 2016

Certificates

CERTIFICATE

This is to certify that this bonafide dissertation in **"PREVALENCE OF PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS PATIENTS"** done by **Dr. HRUDYA VENUGOPAL**, was under my guidance during the academic year 2013 to 2016.

This dissertation has been submitted in partial fulfillment of the requirements for the award of **M.D. Degree in General Medicine, Branch I** by The Tamil Nadu Dr. M. G. R. Medical University, Chennai - 600 032.

Professor & Head,
Department of General Medicine,
Coimbatore Medical College.

Date: 19/9/16

Prof. Dr. KUMAR NATARAJAN, MD.,
CHIEF CIVIL SURGEON
PROF & HOD OF MEDICINE
COIMBATORE MEDICAL COLLEGE HOSPITAL
COIMBATORE
Reg No: 39578

Professor & Guide,
Department of General Medicine,
Coimbatore Medical College.

Date: 19.9.16

Dr.M. RAVEENDRAN, M.D.,
Reg. No. 45738,
Chief Civil Surgeon & A.M.A.
Professor Of Medicine
Coimbatore Medical College & Hospital
COIMBATORE - 641 018.

The Dean,
Coimbatore Medical College.

Date:

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : DR. HRUDYA VENUGOPAL

Course : MD - GENERAL MEDICINE

Period of Study : 2013 - 2016

College : COIMBATORE MEDICAL COLLEGE

Dissertation Topic : PREVALANCE OF PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS.

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted / ~~Not accepted~~ and you are permitted / ~~Not permitted~~ to proceed with the above Study.

DEAN
Coimbatore Medical College & Hospital,
Coimbatore

2. 12. 2014.

INTRODUCTION

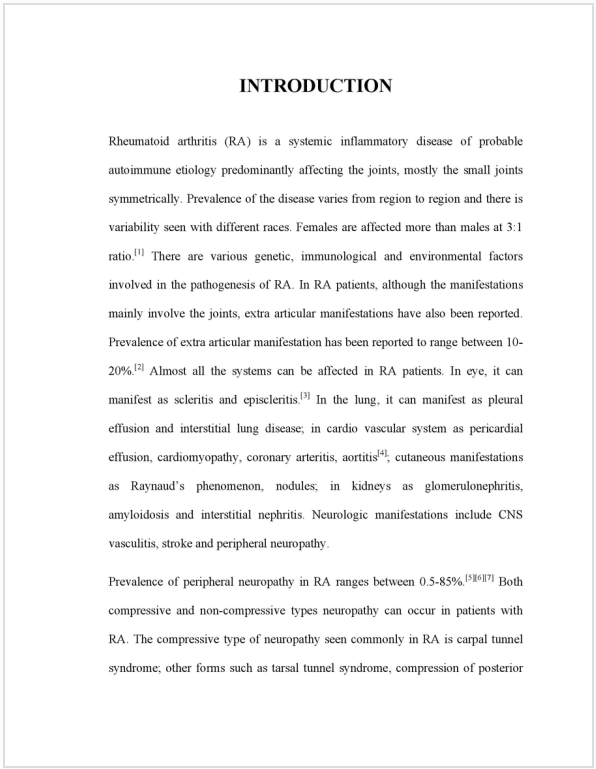
Rheumatoid arthritis (RA) is a systemic inflammatory disease of probable autoimmune etiology predominantly affecting the joints, mostly the small joints symmetrically. Prevalence of the disease varies from region to region and there is variability seen with different races. Females are affected more than males at 3:1 ratio.[1] There are various genetic, immunological and environmental factors involved in the pathogenesis of RA. In RA patients, although the manifestations mainly involve the joints, extra articular manifestations have also been reported. Prevalence of extra articular manifestation has been reported to range between 10-20%.[2] Almost all the systems can be affected in RA patients. In eye, it can manifest as scleritis and episcleritis.[3] In the lung, it can manifest as pleural effusion and interstitial lung disease; in cardio vascular system as pericardial effusion, cardiomyopathy, coronary arteritis, aortitis[4]; cutaneous manifestations as Raynaud's phenomenon, nodules; in kidneys as glomerulonephritis, amyloidosis and interstitial nephritis. Neurologic manifestations include CNS

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201311307.m.d.general Medicine D...
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	Prevalence of peripheral neuropath..
File name:	Prevalence_of_peripheral_neuropa..
File size:	626K
Page count:	79
Word count:	10,474
Character count:	58,902
Submission date:	15-Sep-2015 12:32AM
Submission ID:	569596603



INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease of probable autoimmune etiology predominantly affecting the joints, mostly the small joints symmetrically. Prevalence of the disease varies from region to region and there is variability seen with different races. Females are affected more than males at 3:1 ratio.[1] There are various genetic, immunological and environmental factors involved in the pathogenesis of RA. In RA patients, although the manifestations mainly involve the joints, extra articular manifestations have also been reported. Prevalence of extra articular manifestation has been reported to range between 10-20%.[2] Almost all the systems can be affected in RA patients. In eye, it can manifest as scleritis and episcleritis.[3] In the lung, it can manifest as pleural effusion and interstitial lung disease; in cardio vascular system as pericardial effusion, cardiomyopathy, coronary arteritis, aortitis[4]; cutaneous manifestations as Raynaud's phenomenon, nodules; in kidneys as glomerulonephritis, amyloidosis and interstitial nephritis. Neurologic manifestations include CNS vasculitis, stroke and peripheral neuropathy.

Prevalence of peripheral neuropathy in RA ranges between 0.5-85%.[5][6][7] Both compressive and non-compressive types neuropathy can occur in patients with RA. The compressive type of neuropathy seen commonly in RA is carpal tunnel syndrome; other forms such as tarsal tunnel syndrome, compression of posterior

Declaration

DECLARATION

I solemnly declare that this dissertation entitled **"PREVALENCE OF PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS"** was done by me at **Coimbatore Medical College and Hospital** during the **academic year 2013-2016** under the guidance and supervision of **Prof. Dr. M. RAVEENDRAN M. D.**

This dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University, towards the fulfillment of requirement for the award of M.D. Degree in General Medicine (Branch -I)

Place: Coimbatore
Date: 15.09.2015

Dr. HRUDYA VENUGOPAL

Acknowledgement

ACKNOWLEDGEMENT

At the outset, I would like to express my sincere gratitude to our Dean, **Prof. Dr. EDWIN JOE**, **M.D**., for his permission to conduct this study in Coimbatore Medical College.

I'm immensely grateful and indebted to my **Prof. Dr. KUMAR NATARAJAN M.D.,** Professor and Head, Department of Medicine, Coimbatore Medical College.

It gives me immense pleasure to express my sincere and deep gratitude to my guide, **Prof. Dr. M. RAVEENDRAN M.D.,** Professor, Department of General Medicine, Coimbatore Medical College, for his guidance and constant encouragement throughout the study.

It is with deepest sense of gratitude and respect that I would like to thank my co- guide, **Prof. Dr. MAHESH M.D., D.M.,** Professor, Department of Rheumatology, Coimbatore Medical College, for his constant support, guidance, invaluable suggestions and help that he has rendered through out the study.

I would like to acknowledge with gratitude, the help provided by our Unit Chief **Dr. Sivakumar M.D.,** our unit Assistant Professors - **Dr. Usha Padmini M.D**, **Dr. Balamurugan M.D.** and **Dr Sembakashree M.D**. I would like to thank them for their valuable suggestions throughout the study. I'm indebted to them for being a constant source of inspiration.

I'm gratefully indebted to **Dr. Shobana M.D., D.M.,** Assistant Professor, Department of Neurology, for helping me out with the interpretation of nerve conduction study results, without which I would not have completed my study.

I would also like to thank **Mr. Pradeep**, Technician, Department of Neurology, in helping me in conducting the nerve conduction studies.

I would also like to thank **Dr. Karthikeyan M.D.,** Assistant Professor, Department of PSM, PSGIMS & R, Coimbatore in helping me with the statistical analysis for the study. I would always like to remember with extreme sense of thankfulness for the cooperation and criticism from my fellow post- graduates, my dear seniors and juniors.

I would like to thank my husband, **Dr. Dinoop K.P**. for taking out his time for editing my work and his constant support. I would like to take this opportunity to show my gratitude to my father, **Mr. Venugopalan K.,** my mother **Ms. Sainumole B.,** and my brother **Anand Venugopal** for their never ending support and prayers.

I'm ever grateful to the **ALMIGHTY GOD** for showering his blessings on me and my family and I pray Almighty God to give me the strength to achieve all my endeavors.

Finally, I whole-heartedly thank all **my patients**, who formed the backbone of the study without which this would not have become a reality.

ABBREVIATIONS

RA – Rheumatoid arthritis

CNS – Central nervous system

PNS – Peripheral nervous system

RF – Rheumatoid factor

ESR – Erthrocyte sedimentation rate

CRP – C reactive protein

HLA – Human leucocyte antigen

EBV - Epstein Barr virus

HBV – Hepatitis B virus

HCV – Hepatitis C virus

ACPA – Anti-citrullinated protein antibody

PADI – Peptidyl arginine deaminase

TNF – Tumor necrosis factor

CD – Cluster differentiation

TLR – Toll like receptor

NOD - Nucleotide binding oligomerisation domain like receptors

JAK – Janus kinases

FLS – Fibroblast -like synoviocytes

MMP – Matrix mettalloproteinases

TIMP – Tissue inhibitor of metalloproteinase

PIP - Proximal interphalangeal joint

MCP – Meta carpophalangeal joint

DIP – Distal interphalangeal joint

EAM – extra articular manifestations

HIV – Human immunodeficiency virus

HRCT – High resolution computerized tomography

ILD – Interstitial lung disease

CCP – Citrullinated cyclic peptide

NSAIDS – Non steroidal anti- inflammatory drugs

DMARD – Disease modifying anti-rheumatic drugs

G-CSF – Granulocyte colony stimulating factor

MRI – Magnetic resonance imaging

MRA – Magnetic resonance angiography

NCS – Nerve conduction study

SNAP – Sensory nerve action potential

CMAP – Compound muscle action potential

CV – Conduction velocity

CTS - Carpal tunnel syndrome

HCQ – Hydroxychloroquine

MTX – Methotrexate

SSZ - Sulfasalazine

SLE – Systemic lupus erythematosus

SABE – Subacute bacterial endocarditis

ELISA – Enzyme linked immunosorbent assay

ACR – American college of rheumatology

EULAR – The European league against rheumatism

WBC – White blood cell

IBD – Inflammatory bowel disease

CBC – Complete blood count

LFT – Liver function tests

RFT – Renal function tests

MTB – *Mycobacterium tuberculosis*

DNA – Deoxy ribonucleic acid

GFR – Glomerular filtration rate

ULN – Upper limit of normal

OPD – Out patient department

UL – Upper limb

LL – Lower limb

NCN – Non-compressive neuropathy

CN – Compressive neuropathy

Contents

CONTENTS

List of figures

LIST OF FIGURES

List of tables

LIST OF TABLES

Introduction

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease of probable autoimmune etiology predominantly affecting the joints, mostly the small joints symmetrically. Prevalence of the disease varies from region to region and there is variability seen with different races. Females are affected more than males at 3:1 ratio.[1] There are various genetic, immunological and environmental factors involved in the pathogenesis of RA. In RA patients, although the manifestations mainly involve the joints, extra articular manifestations have also been reported. Prevalence of extra articular manifestation has been reported to range between 10-20%.[2] Almost all the systems can be affected in RA patients. In eye, it can manifest as scleritis and episcleritis.[3] In the lung, it can manifest as pleural effusion and interstitial lung disease; in cardio vascular system as pericardial effusion, cardiomyopathy, coronary arteritis, aortitis[4]; cutaneous manifestations as Raynaud's phenomenon, nodules; in kidneys as glomerulonephritis, amyloidosis and interstitial nephritis. Neurologic manifestations include CNS vasculitis, stroke and peripheral neuropathy.

Prevalence of peripheral neuropathy in RA ranges between 0.5-85%.[5][6][7] Both compressive and non-compressive types neuropathy can occur in patients with RA. The compressive type of neuropathy seen commonly in RA is carpal tunnel syndrome; other forms such as tarsal tunnel syndrome, compression of posterior

and anterior tibial nerves are also reported occasionally. Non-compressive neuropathy like pure sensory, pure motor, mixed neuropathy and mononeuritis multiplex are seen. Causes of peripheral neuropathy in RA include vasculitis[8], compression, amyloidosis and drugs used in the treatment of RA (e.g. infliximab). Pain, paresthesia, muscle weakness are the common manifestations reported RA patients with peripheral neuropathy. It is difficult to distinguish peripheral neuropathy symptoms from RA symptoms. Studies show that most of the RA patients have subclinical peripheral neuropathy. Hence electrophysiological nerve conduction studies are essential in detecting neuropathy in RA patients. These investigations helps in detecting the type of neuropathy and in particular has the advantage of detecting the neuropathy changes in the early course of the disease, especially in cases of compressive neuropathy where timely active intervention can prevent the progression to development of debilitating deformities.

Aims & Objectives

AIM:

To determine the prevalence and type of peripheral neuropathy in rheumatoid arthritis patients

OBJECTIVES:

1. To detect the prevalence of peripheral neuropathy
2. To determine the type of neuropathy and their prevalence
3. To determine the association of peripheral neuropathy with age, sex, gender, duration of disease and laboratory parameters - rheumatoid factor (RF) and erythrocyte sedimentation rate (ESR).

Review of Literature

REVIEW OF LITERATURE

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of autoimmune etiology, mainly affecting the joints. Small joints of hands and feet are mainly involved symmetrically. It is a systemic disorder that has manifestations of extra articular involvement. As it is a disease that mainly involves the joints, it leads to physical disability. In a well-established RA patient, due to physical disability and systemic involvement there will be poor quality of living and socioeconomic disadvantage. Extra articular involvement may be the first presenting symptom in rheumatoid arthritis patients.

Past two decades the severity of the disease has come down, main reason for this trend is due to the early referral to a rheumatologist and due to the better understanding of the disease at genetic level leading to improved treatment modalities.

EPIDEMIOLOGY

RA is a multifactorial disease. Various factors like age, sex, ethnicity, urbanization, genetics, infection and hormonal factors play important role in the development of RA disease.

Age and Gender

Females are affected more than males in 3:1 ratio[1]. Hormones are said to produce the difference in the sex predilection. Mostly affected individuals at observed at the 5th decade of life[9].

Hormones

Estrogen is found to stimulate immune system. So RA is predominant in females and males with reduced androgen. Females presenting with RA during pregnancy, remission of disease has been observed and flare-ups have been reported to occur during the post-partum period.

Genetics

People with HLA-DRB1 in major histocompatibility complex have a strongly predilection to develop RA.[10]

Environmental factors

Strong association has been observed between smoking and RA. People who smoke are found to be at higher risk to develop RA.

Infections with certain organism like Human parvovirus B19, Epstein Barr virus (EBV), *Proteus*, *Escherichia coli*, *Mycobacterium tuberculosis*, Human retrovirus, Alpha viruses and Hepatitis B virus (HBV) have been observed to predispose to the development of RA.

Diet also plays an important role in development of RA. People who take fish, olive oil and vegetables have lesser chance of developing RA. Omega 3 fatty acid, Vitamin D and Vitamin K rich foods protects against development of RA.

Urbanization and pollution has increased the chance of development of RA. Due to the inhalation of pollutants, inflammation develops in local lung tissue, eventually leading to systemic inflammatory response and development of RA.

There is also correlation between birth weight and future development of RA. Birth weight more than 4.54 kg have been associated with 2 fold increased risk of development of RA, compared to birth weight less than 3.8 kg[11].

PATHOLOGY

Pathogenesis of RA involves constant interplay between environment and genetics[12]. Lot of twin studies conducted showed occurrence of RA in 15-30% of concordant twins than in the dizygotic twin which was about 5%[13]. Genetic studies also showed that there are lot of immunological factors which play a role in the pathogenesis of RA. In rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positive patients, association with HLA DRB1 was confirmed, especially patients with amino-acid motif QKRAA also termed shared epitope[10].Presence of this epitope leads to the selection of self reactive T cell clones resulting in autoimmune disorders like RA. Another possible mechanism is molecular mimicry between shared epitope and bacterial antigen. In ACPA

positive individuals, there are various alleles found involved. Various gene-gene interactions have been found to increase the severity of the disease, which can be exemplified by HLA DRB1 and PTPN22.[14]

There is also evidence for RA disease development due to genetic and environmental factor interaction. People who smoke or having exposures to silica are at higher risk for developing RA. Smoking and HLA DRB1 interaction are highly synergistic, leading to production of ACPA. What happens in smoking is that it induces posttranslational modification of certain proteins through PADI4 (peptidyl arginine deaminase 4), leading to citrullination of various mucosal proteins. Citrullinated peptide act as antigen and therefore leads to loss of tolerance to self-antigens.[15][16]

Infections are also postulated to have a role in the development of rheumatoid arthritis. Suspected infectious agents are *Escherichia coli*, *Proteus* species, Epstein-Barr virus, cytomegalovirus and their by-products.[17][18] Gingival infection with *Porphyromonas gingivalis* expressing PADI4 has also been accounted as a causative factor in the development of RA[19]. Molecular mimicry is the possible mechanism in such a causation scenario. Gut flora has also been suspected to play important role in the production of autoimmune antibodies.

Rheumatoid arthritis is much common in women compared to men. It is found that the onset of RA is related with adverse life events. It has been linked to hypothalamo-pituitary adrenal axis and cytokines which was found in animal

models[20] In mouse models, neuro-immunologic modulators was found to initiate the disease locally or centrally.

In RA patients, long before the appearance of symptoms, antibodies to ACPA and RF are positive and until now there is no explanation why loss of self-tolerance lead to localized onset of joint inflammation. (Figure 1)

SYNOVIAL IMMUNOLOGIC PROCESS AND INFLAMMATION

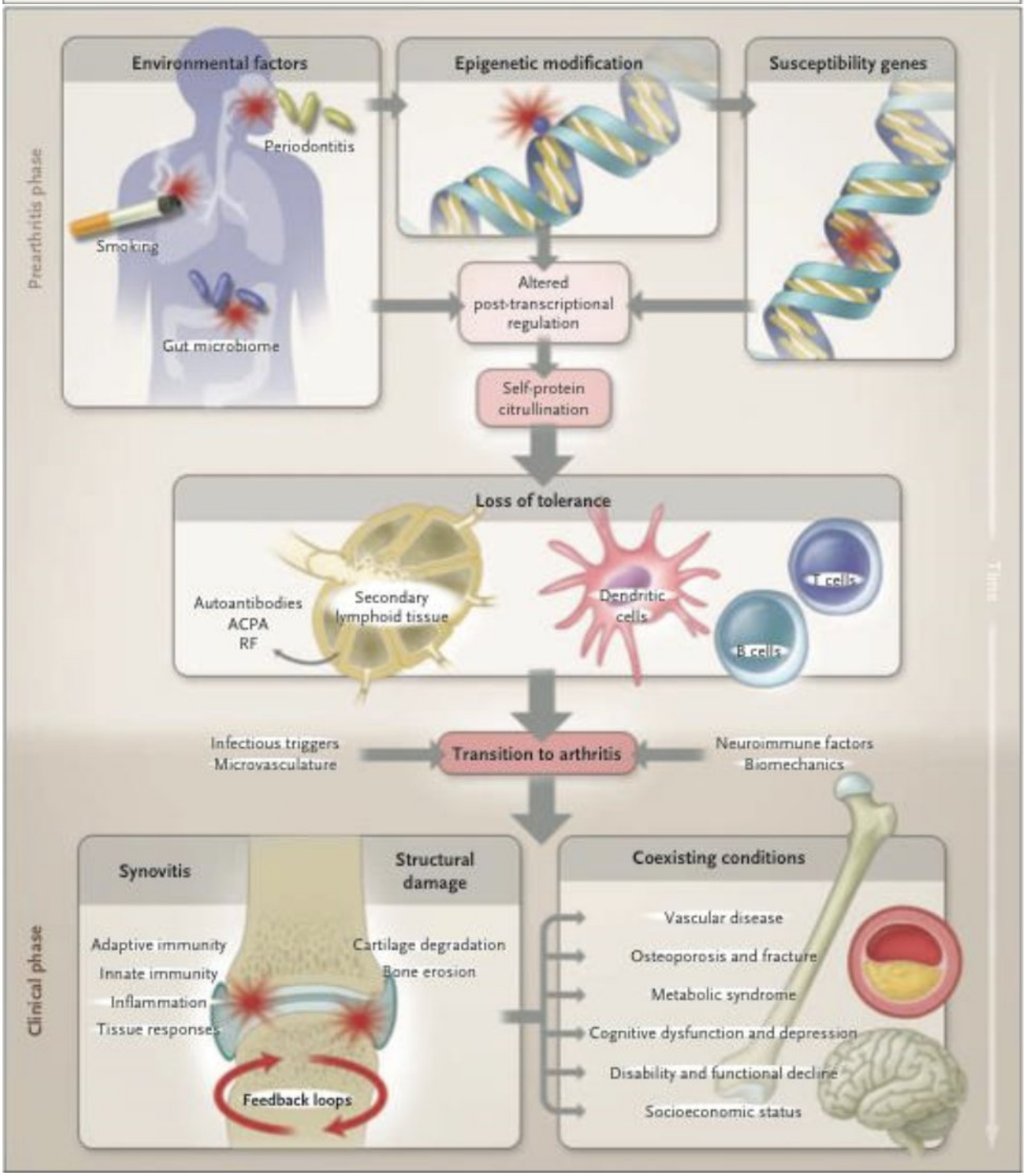
Synovitis occurs due to infiltration of leukocyte into the synovium. Infiltration is made possible by the endothelium activation, which expresses various adhesion molecules like integrin, selectin and immunoglobulins. There is increased vascular neogenesis seen in the synovium due to hypoxic conditions & cytokines; and lymphangiogenesis is decreased. Thus it eventually leads to synovitis.[21][22]

Adaptive immune pathway

In RA patients, autoantibodies are seen in the circulation even before the symptoms appear. So adaptive immunity play an important role in the early disease process. Role of T cells in the pathogenesis of RA is not clearly understood. Synovium in RA patients are rich in myeloid, plasmacytoid and dendritic cells which express cytokines, HLA class ll molecules, co-stimulatory molecules which are essential for stimulation of T cells[23][24].T helper cells are responsible for inflammation. TH 17 is more potent than TH1 and it produces

Figure 1. Multistep Progression to the Development of Rheumatoid Arthritis.

Environment–gene interactions described in the text promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification. This anticitrulline response can be detected in T-cell and B-cell compartments and is probably initiated in secondary lymphoid tissues or bone marrow. Thereafter, localization of the inflammatory response occurs in the joint by virtue of poorly understood mechanisms that probably involve microvascular, neurologic, biomechanical, or other tissue-specific pathways. Synovitis is initiated and perpetuated by positive feedback loops and in turn promotes systemic disorders that make up the syndrome of rheumatoid arthritis. ACPA denotes anti–citrullinated protein antibody, and RF rheumatoid factor.



TNFα, interleukin 17A, 17F, 21 and 22[25][26].There is another subset of T cell population named T regulator cells, role of these is to counteract the effect of T helper cells (i.e) suppression of inflammation. When there is an imbalance between the T helper cell and the regulatory T cell then it leads to inflammation.[27] TNF-α along with interleukin-17 helps in the activation of chondrocytes and fibroblasts[28]. Macrophage- derived TNF-ß helps in the differentiation of Th17 and suppress differentiation of regulatory T cells, thus leading to shift of the milieu towards inflammation. Humoral immunity also plays an important role in pathogenesis of RA. The synovium and juxta-articular area are rich in plasma cells and blast cells and hence there is definite role for CD20 in RA pathology as it is evidenced by the fact that RA patients respond better to Rituximab treatment[29].

Innate immunity

Synovium of RA patients contains innate effector cells like mast cells, macrophages, naïve T cells. Synovial fluid containing neutrophils and macrophages play a major role in innate immunity. It is activated through Toll Like Receptors (TLRs), Nucleotide binding oligomerisation domain, (NOD) like receptors (NLRs) which recognize the pathogenic molecule of bacteria and virus.[30] Activation of macrophages results in the release of reactive oxygen species, nitrogen intermediates and protease, which destroys the matrix, enhancing phagocytosis and antigen presentation. Activation of neutrophils causes release of

reactive oxygen species, prostaglandins and proteases[31]. Mast cell which is activated through TLRs produces vasoactive amines and cytokines.[32][33] So what can be concluded is that by blocking the TLRs and NLR pathway through biological agent the inflammatory process of RA can be reduced.

Cytokines and Intracellular signaling Pathway

Cytokines are produced by the cells in the synovium and synovial fluid, like macrophages, mast cells, neutrophils, T and B cells. In the synovium, various patterns of cytokines are seen at different phase of RA. TNF-α is mainly involved in the local inflammatory process of synovium by inducing angiogenesis, suppression of T regulatory cells, expression of endothelial adhesion molecule and protection of synovial fibroblast.[34][35] Interleukin-6 plays an important role in systemic inflammatory process such as increased expression of acute phase reactant proteins, cognitive changes, alteration in lipid metabolism, anemia and fever. Disease-making role of TNF-α and IL-6 is confirmed by reduction in inflammatory response by administering biological agent that blocks their activity. Chondrocytes, osteoclasts, endothelium and leukocytes are activated by interleukin-1 family.[36][37] Intracellular pathway and Janus Kinase pathway are involved in the formation of various cytokines, growth factors and interferons which contributes to the development of RA disease. This was found out in the trial conducted that showed decrease disease activity in individuals who was treated with JAK1and 3 inhibitor.

Mesenchymal tissue response

Normally in synovium there are macrophages, fibroblast-like synoviocytes (FLS) which is derived from mesenchyma. In RA patients, what happens in the synovium is that FLS acquires a property by which it can act independently, there is no contact inhibition, anchorage independence, release of cytokines, adhesion molecule, matrix-metalloproteinase (MMP), Tissue inhibitors of metalloproteinase (TIMP).[38] They promote a microenvironment for T & B cell.[39] There is decreased apoptosis and hence proliferation results. There are various mechanisms by which apoptosis is reduced 1) Mutation in tumor-suppressor gene p53,[40] 2) Heat shock proteins which helps in the survival of FLS,[41] 3) Function of endoplasmic reticulum is altered by synoviolin, a E3 ubiquitin thereby balance between proliferation and apoptosis is altered.[42] Mesenchymal cells can infiltrate the synovium that also adds to the hyperplasia.

Structural Damage

Cartilage Damage

Cartilage damage is mainly due to synovial hyperplasia. There is alteration of protein binding ability of the cartilage; there is excessive influx of FLS, which in turn produces MMP. These MMP degrade type ll collagen thus reduces the ability to hold water and hence decrease the lubrication of the joint causing biomechanical dysfunction.[43] Natural inhibitors of proteinase like TIMP fail to

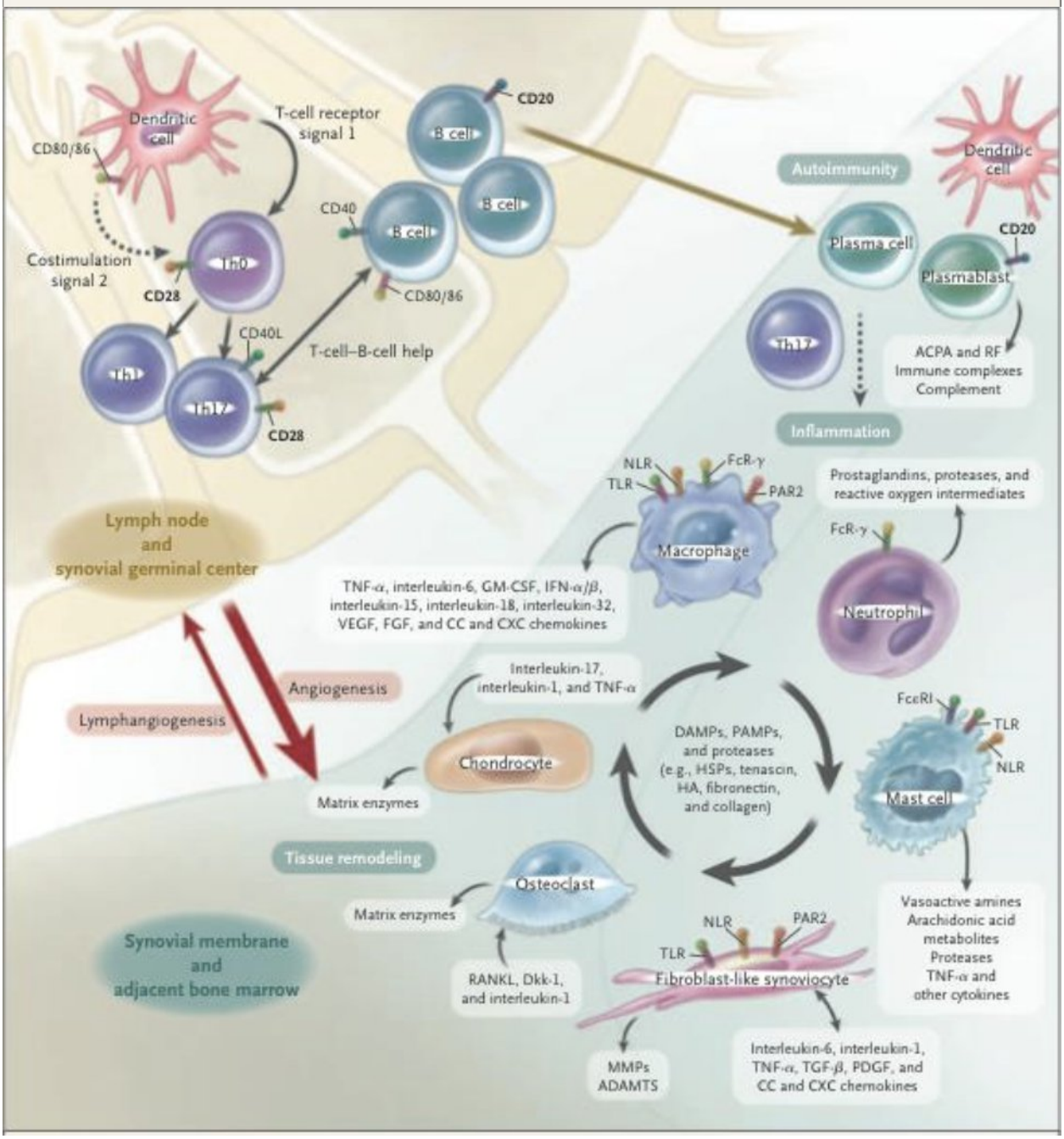
act, thus adding on the destructive process Inflammatory cytokines in the synovium cause apoptosis of the chondrocytes and thus results in the destruction of the synovium, which is seen as reduction in joint space in joint radiography.

Bone erosion

In 80% of the people with RA, bony erosion is seen within one year of the disease development.[44] This rapid progression is due to the ongoing inflammatory process in the body. Osteoclasts are activated by TNF-α and IL-1, 6, 17.[45] Certain mediators are produced by cytokines like dickkopf and frizzled related protein -1 which inhibits the differentiation of mesenchymal cells into chondroblasts and osteoclasts.[46] One another factor which favor erosion is the mechanical factor. In joints with increased mobility (for e.g. 2^{nd} and 3^{rd} metacarpals) wear and tear occurs faster. Due to the erosion, cortical bone marrow gets infiltrated with T & B cells eventually causing replacement of marrow fat with inflammatory cells.[47] Still it is unclear whether inflammation starts in the marrow, erodes the bone and reaches the synovium or vice versa. (Figure 2)

Figure 2. Adaptive and Innate Immune Processes within the Joint in Rheumatoid Arthritis.

The costimulation-dependent interactions among dendritic cells, T cells, and B cells are shown as occurring primarily in the lymph node; these events generate an autoimmune response to citrulline-containing self-proteins. In the synovial membrane and adjacent bone marrow, adaptive and innate immune pathways integrate to promote tissue remodeling and damage. Positive feedback loops mediated by the interactions shown among leukocytes, synovial fibroblasts, chondrocytes, and osteoclasts, together with the molecular products of damage, drive the chronic phase in the pathogenesis of rheumatoid arthritis. ADAMTS denotes a disintegrin and metalloprotease with thrombospondin-1–like domains, DAMP damage-associated molecular pattern, Dkk-1 dickkopf-1, FcR Fc receptor, FcεRI high-affinity IgE receptor, FGF fibroblast growth factor, GM-CSF granulocyte–macrophage colony-stimulating factor, HA hyaluronan, HSP heat-shock protein, IFN-α/β interferon-α/β, MMP matrix metalloproteinase, NLR nucleotide-binding oligomerization domain–like receptor, PAMP pathogen-associated molecular pattern, PAR2 protease-activated receptor 2, PDGF platelet-derived growth factor, RANKL receptor activator of nuclear factor κB ligand, TGF-β transforming growth factor β, Th0 type 0 helper T cell, Th1 type 1 helper T cell, Th17 type 17 helper T cell, TLR toll-like receptor, TNF-α tumor necrosis factor α, and VEGF vascular endothelial growth factor.



CLINICAL FEATURES

Rheumatoid arthritis patients usually present with complaints of symmetrical joint pain, early morning stiffness lasting for more than one hour, which gets better after doing some physical activity. Inflammation of the joints, bursa and tendon produces the symptoms. Joints involved are small joints of the hand particularly the proximal interphalangeal joint (PIP) and metacarpophalangeal (MCP) joint. Distal interphalangeal (DIP) joint is very rarely involved. Large joints like knee and shoulders are involved only in well-established cases of rheumatoid arthritis later in the course of the disease.

Joint deformities are seen in well-established case of rheumatoid arthritis in which there is progressive destruction of the joints and soft tissue. Boutonniere deformity (flexion of PIP joint with hyperextension of DIP joint), swan necked deformity (hyperextension of PIP joint with flexion of DIP joint), Z-line deformity (subluxation of the first MCP joint with hyperextension of the PIP joint) are some of the named deformities in RA. Due to subluxation of the MCP joint along with proximal phalanx there is ulnar deviation. Some patients develop pesplanovalgus (flat foot) due to the involvement of the ankle and midtarsal region. C1 and C2 vertebra can be involved leading to compressive myelopathy. In less than 10% of the RA patients, subluxation of the atlantoaxial joint can occur. Thoracic and lumbar vertebrae are usually spared. Temperomandibular joint can be involved

with significant radiological abnormality but usually there wont be any functional impairment.

RA patients can present with fever, fatigue, malaise & depression and in severe cases with cachexia. Sometimes these symptoms can precede onset of joint symptoms.

EXTRA ARTICULAR MANIFESTATIONS

Prevalence of extra articular manifestation in RA patient ranges between 40-70%. Extra articular manifestations can involve skin, eyes, heart, lungs and nervous system. Severity of the extra articular manifestation depends on various factors like RF positivity, ANA positivity, smoking and early onset of the disease.[48] There is no predilection for male or female for development of EAM. Some of the recent studies have shown link between EAM and polymorphisms in the promoter site of endothelial nitric oxide synthase gene. This polymorphism 786c/c is seen in RA patients than in normal individual and is linked with increased risk of EAM.[49]

Rheumatoid vasculitis is the cause for EAM in a majority of the cases. It can lead to various cutaneous and organ-specific manifestations. Vasculitides mainly affects the skin and peripheral nerves. CNS, lungs, heart are rarely affected.[50] Other comorbidities such as diabetes, neoplasm and HIV should be ruled out before branding it as rheumatoid vasculitis.

Mainstay of treatment for RA vasculitidis is steroids and cytotoxic drugs.

CUTANEOUS MANIFESTATIONS

Skin is the most commonly involved organ. Rheumatoid nodules, vasculitic ulcers, Raynaud's phenomenon, and in patients receiving methotrexate can develop a condition called accelerated rheumatoid nodulosis.

Rheumatoid nodules

These are painless subcutaneous nodules of size >5mm, which are usually seen in areas of increased pressure, external irritation such as extensor aspect of the forearm, fingers, occiput, heel, sacral prominence, buttocks, nose and ear. Some times nodules will be seen in viscera like lung, pleura, pericardium, synovium and meninges. Rheumatoid nodules are seen in 30% RA patients. People who are RF positive have higher chance of developing rheumatoid nodules.[51] Smoking and homozygosity for HLA DRB1 gene are the 2 other independent risk factors for developing rheumatoid nodule.[52]

Microscopically, RA nodule has three zones - central necrotic area containing cellular debris, collagen, fibrin, which is surrounded by palisading macrophage, which is further surrounded by tissue infiltrated by perivascular migration of lymphocytes, plasma cells, histiocytes. Pathogenesis of the nodule is attributed to IgM. RF containing immune complexes & complement activation are observed at the site of endothelial injury.[53]

Rheumatoid nodules need not be treated, unless any ulceration or any compression of the nerve occurs.

Raynaud's phenomenon

About 5-17% of the RA patient develop Raynaud's phenomenon.[54] It is due to the vasospasm of vessels of fingers or toes to cold or emotional stress. It does not affect the function of hands.[55] Late onset of development of Raynaud's phenomenon in RA patients denotes onset of more severe disease.[56]

PULMONARY MANIFESTATIONS

About 5-10% of the RA patients have pulmonary manifestation,[57] which is often the major cause of morbidity and mortality. Manifestations can be varied like interstitial lung disease, rheumatoid nodule, pleural effusion, pulmonary vasculitides or small airway disease. Usually pulmonary nodules are asymptomatic but there is increased chance for pneumothorax and infections. Sometimes solitary pulmonary nodule can be mistaken for lung cancer. HRCT is the best investigation by which ILD can be picked up even before symptoms develop.[58] There is a study that shows around 50% of the RA patients revealed ILD whereas only 10% were symptomatic. Mainstay of treatment includes steroids and cyclophosphamide. Response to these agents is better than in patients with idiopathic pulmonary fibrosis. Anti CD-20 therapy shows some benefit.[59] Role of TNFα not yet studied.

CARDIAC MANIFESTATIONS

Almost all parts of the heart like pericardium, myocardium, coronaries, aorta can be involved.[4] Patients with cardiac involvement have poor outcome.[60] Most common involved site is the pericardium and symptomatic pericarditis is seen in about 1-4% of the RA patients.[61] It is mostly seen in seropositive male RA patients. Myocarditis, coronary arteritis and aortitis occur very rarely. Coronary arteritis and aortitis occur due to rheumatoid vasculitis or due to accelerated atherosclerosis, which is seen in RA patients. It is mostly found during autopsy. Reason for early cardiac involvement in RA involves numerous factors like altered endothelium function, genetics, smoking habit, presence of auto antibodies to CCP and expansion of circulating CD4+CD28+T cells.[62][63][64] Asymptomatic cardiac involvement does not require treatment. Pericarditis with dull chest pain without hemodynamic compromise can be treated with NSAIDS and steroids. Recurrent pericarditis can be treated with cyclophosphamide. Patient with constrictive pericarditis and hemodynamic instability require immediate emergency intervention.

RENAL MANIFESTATIONS

Renal involvement is very rare in rheumatoid arthritis patients. Among RA patients with renal involvement most commonly seen presentation is glomerulonephritis (65%), followed by secondary amyloidosis (25%) and very

rarely interstitial nephritis.[65] Secondary amyloidosis is seen in chronic inflammatory disease conditions. Main risk factor for amyloidosis is the chronicity of disease (7-10yrs) and disease uncontrolled with treatment. Secondary amyloidosis is due to the deposition of Amyloid A fibrils. It is derived from degradation of serum AA, an acute phase reactant produced by liver. Secondary amyloidosis is not seen in all patients with rheumatoid arthritis, but only in some patients with high titers of serum RF. This suggests that there are other factors contributing for their deposition. Genotype SAA1 is associated with the early occurrence of amyloidosis.[66][67][68] Treatment for amyloidosis is cyclophosphamide accompanied with steroids, chlorambucil and colchicine.

OCULAR MANIFESTATIONS

Rheumatoid arthritis patients can develop eye involvement like secondary sjogrens, episcleritis, scleritis, keratitis and retinopathy. Among these, secondary sjogrens and episcleritis are the most common manifestations.[3] Episcleritis is of three types, diffuse, nodular, necrotizing (scleromalacia performans). Scleromalacia is seen in <1% of the RA patients and it is the most severest form. It leads to thinning of the sclera and is seen in female patients with high titers of RF.[69] This results due to the vasculitis and deposition of the immune complexes. This condition is painless and can lead to perforation of the sclera. Treating with DMARD's can prevent this complication. Use of anti TNFα and AntiCD-20 also results in decreased incidence of eye manifestations.[70]

HAEMATOLOGIC MANIFESTATIONS

People with RA can be seen with massive splenomegaly, neutropenia, which is called Feltys' syndrome.[71] In 75% of the people affected with feltys syndrome, skin nodules are seen.[71] People affected with feltys get recurrent bacterial infection due to reduced neutrophils and is the major cause of mortality. Neutropenia responds to Granulocyte colony stimulating factor (G-CSF) therapy. Response are noticed when it was combined with DMARD's or low dose of methotrexate.[72] Splenectomy is avoided to the maximum as chance of infection increases

NERVOUS SYSTEM MANIFESTATIONS

Central Nervous System

Relapsing focal neurological deficits, neuropsychiatric problems, meningoencephalopathy, stroke headaches can be seen rarely occurring in RA patients. [73] These symptoms are due to CNS vasculitis.[74] The diagnosis is usually supported by MR imaging and MR angiography. Most of the symptoms resolve by treating with Methyl prednisolone or cyclophosphamide pulse therapy. Anti-TNF α can be used in people resistant to conventional treatment.

Peripheral Nervous System

In RA patients, the most common neurological manifestation is peripheral neuropathy. Both compressive and non-compressive neuropathies are seen in RA patients, out of which compressive neuropathy is the most common. Nerve conduction studies (NCS) have been widely used currently in determining peripheral nervous system dysfunction.

The three main mechanisms known to affect peripheral nerves are

1. Axonal degeneration – detected by measuring the reduction in amplitude of sensory nerve action potential (SNAP) and compound muscle action potential (CMAP)
2. Demyelination – detected by measuring the reduction in conduction velocity and
3. Conduction block – detected by recording a drop in the CMAP amplitude

Nerve conduction studies (NCS) can only evaluate large myelinated fiber functions and hence cannot be utilized in polyneuropathies affecting predominantly the small fibres. Since the neuropathic changes observed in rheumatoid arthritis patients are seen predominantly in large myelinated fibres, NCS are extensively used in the evaluation of peripheral neuropathy in rheumatoid arthritis (RA) patients.

Measurement of motor nerve conduction. (Figure 3 & 4)

CMAP latency - Time between stimulus onset and onset of negative peak

CMAP amplitude - Height of the negative peak from baseline or the difference between negative and positive peaks.

CMAP area - Area under the negative peak waveform

CMAP duration - Time from onset of the negative peak to return to baseline of the end of the potential

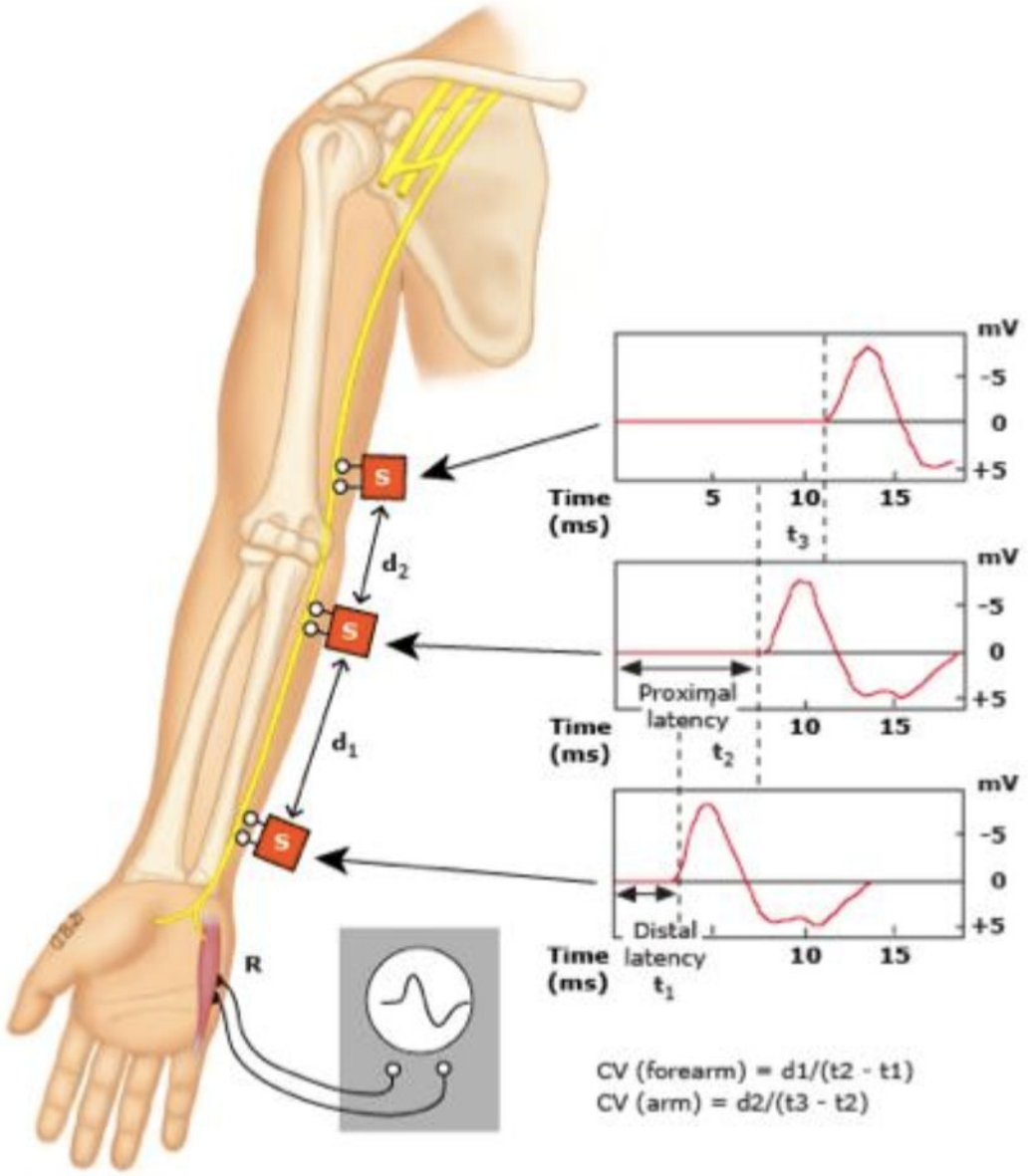
Motor conduction velocity = d/(proximal latency - distal latency). The units are millimeters/millisecond (mm/msec), or meters/second (m/s).

Measurement of sensory nerve conduction. (Figure 5)

Sensory conduction velocity - Dividing conduction distance by conduction time between stimulating and recording electrodes.

The compound muscle action potential (CMAP) is measured in millivolts (mV), whereas the sensory nerve action potential (SNAP) is measured in microvolts (microV).[75]

Motor nerve conduction study

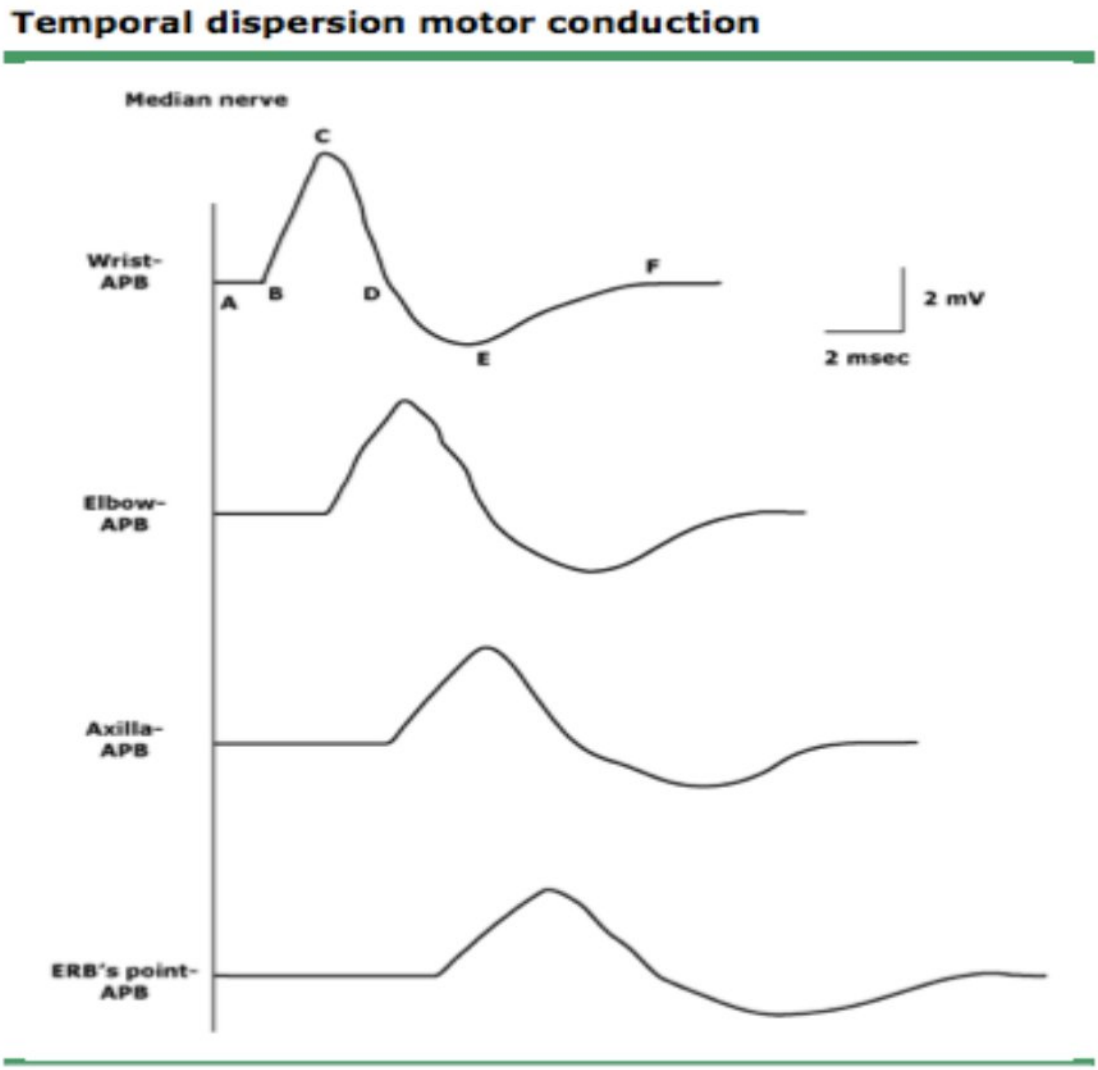


Stimulation at different proximal sites along the ulnar nerve while recording from the abductor digiti minimi muscle allows the conduction velocity (CV) of the motor neurons to be calculated.

Courtesy of Shahram Khoshbin, MD.

Figure 3.

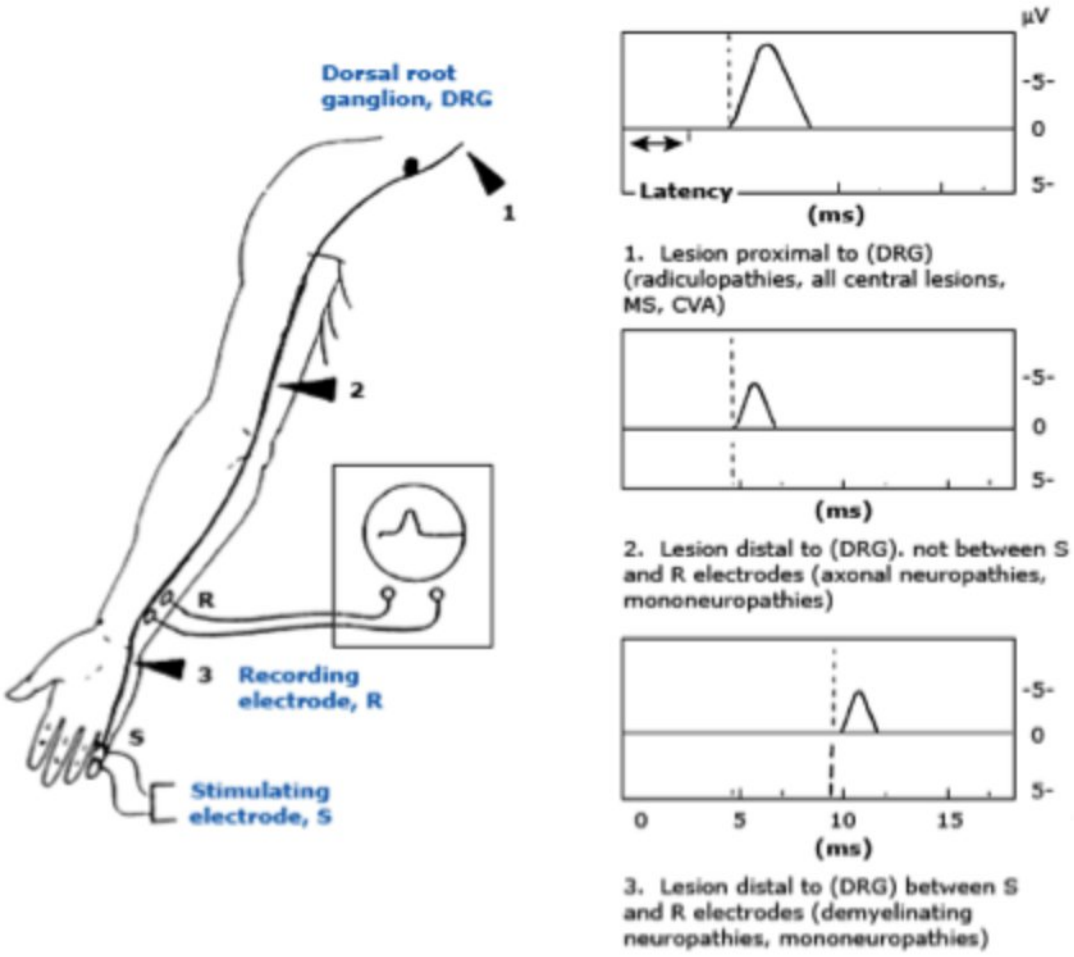
Figure.4



With increasing lengths of nerve segment between stimulating and recording electrodes, temporal dispersion increases and amplitude decreases.

A: Stimulus onset.
B: CMAP onset.
C: Peak amplitude of negative phase.
D: Return to baseline.
E: Peak of positive phase.
F: Return to baseline.
A-B: Latency.
B-C: Rise time.
B-C-D: Area under the curve.

Sensory nerve conduction study



Recording of the sensory action potential is helpful in determining the site of nerve injury particularly in those with lesions resulting in sensory symptoms. This illustration depicts a sensory nerve conduction study of the ulnar nerve. Normal latency is seen with lesions of the central nervous system or those that are proximal to the dorsal root ganglion (arrowhead number 1). A more distal lesion (arrowhead number 2) results in a decreased amplitude but normal conduction velocity. Either a compressive mononeuropathy (arrowhead number 3) or generalized demyelinating peripheral neuropathy results in a decrease in both amplitude and conduction velocity.

Courtesy of Shahram Khoshbin, MD.

Figure 5.

Compressive Neuropathy or Entrapment Neuropathy

Entrapment neuropathy is seen in RA patients with severe disease. In patients with increased severity of the disease, there are inflamed tendon sheaths, ligament, synovium and joint deformity which will in turn compress the peripheral nerve passing adjacent to the joints causing neuropathy. Sometimes rheumatoid nodules itself can compress upon the peripheral nerves causing the symptoms. Age, duration of the disease, gender, and seropositivity does not have any correlation with development of compressive neuropathy.

Carpel Tunnel Syndrome (CTS)

The most common compressive type of neuropathy seen in RA patient is carpel tunnel syndrome. Various literature shows the prevalence of CTS as 23-69%.[76][77][78][79] CTS occur probably due to finger flexor tenosynovitis as these tendon pass through the carpel tunnel.

Tarsal Tunnel Syndrome. [80]

It is caused due to the entrapment of posterior tibial nerve in the tarsal tunnel near the medial malleolus. Inflammation of the flexor retinaculum, tenosynovitis and valgus deformity in RA patients can lead to tarsal tunnel syndrome. Due to the entrapment, there is wasting and weakness of the foot muscles in long standing cases. Symptoms such as pain, paresthesia can occur in the foot. All RA patients with entrapment need not be symptomatic.

Occurrence of entrapment neuropathy other than carpel tunnel syndrome and tarsal tunnel syndrome are very rare. Entrapment neuropathy has been reported in anterior and posterior interosseus nerve, ulnar, common peroneal and tibial nerves. [81][82][83][84].There is an entity called double crush syndrome which is actually cervical spine involvement with nerve entrapment along with entrapment of nerve elsewhere in the body.

Treatment of compressive neuropathy

Mainly conservatively managed with splints, anti-inflammatory medications, analgesics and treatment of the cause. Surgical management is required only when there is motor or sensory deficit, which is worsening even after taking conservative measures.

Non-compressive Neuropathy

Distal sensorineuropathy, combined neuropathy are seen in RA patients. The reasons for development of non-compressive neuropathy have been identified as vasculopathy and vasulitis.[8][85]

Distal Sensory Neuropathy

Symptoms of sensory neuropathy are difficult to distinguish from arthritis symptoms. Patients complain of symmetrical paresthesia and burning sensation more in lower limbs compared to upper limbs. On examination, patients will have decreased vibration, position and pin prick sensation. There are various studies that suggest that there is no correlation between disease duration and development of neuropathy. Sural nerve biopsy shows mild endarteritis or normal vasculature of vasa nervosum. Overall there is good prognosis for the sensory neuropathy as it doesn't progress to severe neuropathy. Almost 75% of the patients with distal sensory neuropathy recover either completely or partially.

Combined Sensorimotor Neuropathy

It is a more aggressive form of neuropathy, usually seen in seropositive cases, male gender and RA patients with skin manifestations like nodules, Raynaud's phenomenon, constitutional symptoms, features of vasculitis like purpura, livedoreticularis. Mostly people are asymptomatic. People can present with symptoms like asymmetrical paresthesia and weakness, wrist drop and foot drop. In such patients there will be high RF titers, decreased complement level and high titers of immunoglobulin. Prognosis is bad since this type of neuropathy can progress to severe form. Rarely some people improve but they can have residual sensory deficit and motor weakness. Nerve conduction studies show axonal degeneration and demyelination.

In RA patients, increased cardiovascular reflexes is reported which supports for presence of autonomic neuropathy.

Primary pathology behind neuropathy is vasculitis of epineural vessels leading to axonal degeneration and demyelination. Biopsy of vessel shows fibroid necrosis of media with infiltration of polynuclear cells, eosinophils or lymphocytes, perivascular infiltrates with lymphocytes, intimal proliferation/fibrosis. Arterial inflammation can be immune complex mediated, which is evidenced by the deposition of IgG, IgM and complement in the area of necrosis.

Treatment for neuropathy is given to RA patients with immune-mediated necrotizing vasculitis. Patients are treated with either oral or intravenous cyclophosphamide and prednisolone. Some studies show reversion of neuropathy with TNF-α inhibitors.

Neuromuscular Disorders

In RA patients, neuromuscular diseases like myopathy and myositis are seen.

Disuse Atrophy

Due to joint synovitis in RA patients, movements are restricted which leads to disuse atrophy of muscles. This event can be prevented by early control of

inflammation by anti-inflammatory agents, adequate analgesics and implementation of muscle strengthening exercised.

Denervation Atrophy

Muscles can get atrophied due to denervation as seen in mononeuritis multiplex due to vasculitis leading to axonal degeneration and demyelination. Biopsy of the muscle usually does not show any inflammation. Treatment of denervation atrophy is by control of vasculitis by controlling inflammatory process.

Muscular dystrophy-like myopathy

This type of myopathy in RA is similar to muscular dystrophy both clinically and pathologically. It is characterized pathologically by muscular atrophy, difference in caliber of fiber, replacement of muscles with adipose tissue and fibrosis of muscle fiber. Innervation to the muscle is not compromised.

Glucocorticoid induced myopathy

Due to the chronic use of corticosteroids in RA patients for controlling inflammation, development of proximal muscle weakness can result. Biopsy of the muscle shows type ll muscle fiber atrophy. Mainstay of treatment is tapering of steroids and muscle strengthening exercises.

Myositis

There is infiltration of endomysium, perimysium and perivascular areas with lymphocytes, plasma cells and mononuclear cells. Myositis in RA is patchy and less severe than that observed in inflammatory polymyositis. It will respond to low dose steroids compared to the later. Treatment for both is similar.

Amyloidosis

Due to the inflammatory process going on in the body there can be deposition of amyloid in the central or peripheral nervous system. These can produce peripheral neuropathy and CNS vasculitis.

Drugs for RA affecting nervous system

Drugs used in RA can produce various neurological manifestations. NSAIDS can produce symptoms like headache, aseptic meningitis. Hydroxychloroquine (HCQ) can produce symptoms like seizures, neuromyopathy and tinnitus. Methotrexate (MTX) can cause side effects like headache and confusional state. Leflunomide can cause peripheral neuropathy; TNF-α inhibitors can cause progressive multifocal leukoencephalopathy and peripheral neuropathy. Glucocorticoids can produce proximal muscle weakness, depression and psychosis.

Diagnosis of RA

Diagnosis of RA is mainly based on history, physical examination, certain laboratory parameters like ESR, CRP, RF, anti-CCP antibodies and duration of the disease.

Laboratory features

RA is a systemic inflammatory disease in which there is elevated ESR and CRP. Their elevation shows ongoing inflammatory activity in the body and thus it acts as an indicator for supporting RA diagnosis as well as to know the effectiveness of the treatment undertaken for the disease.

RF can be found in the sera of the patient as determined by IgM, IgA and IgG isotypes, of which IgM isotype is the commonest in RA patients. RF positivity is not must for the diagnosis of RA. It can be falsely positive in Sjogrens syndrome, SLE, Type ll mixed essential cryoglobulinemia as well as chronic infections with hepatitis B, hepatitis C, sub acute bacterial endocarditis (SABE). RF factor can be some times positive in normal individuals also.

Anti –CCP antibody positivity can be seen in RA patients. It is detected by ELISA method. There is 95 to 98% RA diagnostic specificity for anti CCP antibodies.[86][87][88][89] Hence, a person with early feature of inflammatory arthritis with positive anti-CCP antibodies helps differentiation from other arthritis.

Table 1: ACR-EULAR CRITERIA (2010) FOR CLASSIFICATION OF RA[90][91]

JOINT INVOLVEMENT	1 large joint(shoulder,knee,hip,ankle,elbow)	0
	2-10 large joints	1
	1-3 small joints(MCP,PIP,Thumb,IP,MTP,wrist)	2
	4-10 small joints	3
	>10joints(at least 1 small joint)	5
SEROLOGY	Negative RF and Negative ACPA	0
	Low positive RF or Low positive ACPA(.>3 times ULN)	2
	High positive RF or High positive ACPA(>3 times ULN)	3

ACUTE PHASE REACTANTS	Normal CRP and normal ESR Abnormal CRP or abnormal ESR	0 1
DURATION OF SYMPTOMS	<6 weeks >6 weeks	0 1

A score of ≥ 6 fulfills the requirement for definitive diagnosis of RA[92]

This criteria helps us to pick up RA patients very early so that early treatment can be instituted thereby preventing the formation of deformity and debility.[93]

Synovial Fluid Analysis

It is done only when there is confusion in diagnosis. In RA patients, synovial fluid can contain WBC's ranging from 5000-50000/μL, mostly neutrophils. In osteoarthritis, WBC's will be less than <2000/μL. Synovial fluid analysis helps to differentiate RA from crystal-induced arthritis or arthritis due to infection origin.

Joint Imaging

X-ray of the affected joints is the most common imaging modality used in the diagnosis of RA. Radiographic imaging of affected joints can reveal bone erosions, effusion, deformity (subluxation of joint and collapse), osteopenia and joint space reduction. MRI and ultrasonography helps to detect tenosynovitis,

synovitis and joint effusion. Currently, musculoskeletal ultrasound and power Doppler are increasingly used to detect bone erosion and synovitis.

Differential Diagnosis for RA

Reactive arthritis and arthritis of inflammatory bowel disease (IBD),

Polymyalgia rheumatica,

Viral polyarthritis – Hepatitis B, Hepatitis C, Alpha viruses[94][95] like chikungunya, rubella[96] and parvovirus[97],

Palindromic arthritis,

Paraneoplastic arthritis,

Rheumatic fever,

Lymes disease,

Crystalline arthritis,

Psoriatic arthritis[98]

Infectious arthritis and

Osteoarthritis

History taking, clinical examination and appropriate investigations helps in distinguishing these diagnosis from RA.

MANAGEMENT OF RHEUMATOID ARTHRITIS IN ADULTS[99][100]

Early diagnosis of RA and prompt treatment to reduce the inflammation is very important in preventing the progress of the disease and associated deformity and debility. In recent years, RA patients going for severe complication of RA have markedly reduced due to the early diagnosis and newer therapeutic modalities. It is advisable to refer patients for treatment to rheumatologist as many data shows better management and outcome of the disease.

Non-Pharmacological Measures

Patients should be educated regarding the disease, its complications, need for drug compliance, follow up, watch for side effects of the drugs prescribed. Adequate nutrition, rest, psychosocial support, physical and occupational therapy are key for better prognosis in RA patients. Immunisation is very important as many of the drugs employed for treatment of RA leads to reduction in immunity.

Pharmacological Therapy

Before starting treatment, RA patients should be evaluated as drugs involved in treatment are immunomodulatory and are associated with side effects. So all patients should undergo complete haemogram (CBC), C-reactive protein (CRP), Erythrocyte sedimentation rate(ESR), Serum creatinine, aminotransferases must be checked. Viral markers of Hepatitis such as HBsAg, HCV should be checked

prior start of therapy. In individuals with positive viral marker adequate treatment should be undertaken for these viral diseases before commencement of RA treatment.

Ophthalmological assessment needs to be done in order to assess the fundus and visual acquity. Drugs like hydroxychloroquine (HCQ) used in RA treatment can affect eyes and hence baseline evaluation is very important for follow-up of such patients.

All newly detected RA patients are required to be screened for latent tuberculosis prior start of treatment. Screening for tuberculosis are performed using chest X-ray, mantoux test or interferon gamma release assays. Treatment with DMARD's increases the susceptibility for *Mycobacterium tuberculosis* (MTB) infection, and the only drug, which is found to be exceptional, is Rituximab.

Treatment of choice is based on the stage of the disease, patient's affordability, and their choice. Treatment of RA is usually a combination of anti-inflammatory and disease modifying agent for rheumatoid disease (DMARD).

Anti-inflammatory agents used are non-steroidal anti-inflammatory drugs (NSAID's) and glucocorticoids.

DMARD's are of 2 types: Biological and non-biological agents.

Non-biological disease modifying agents (conventional and synthetic) used are methotrexate, leflunomide, hydroxychloroquine and sulfasalazine.

Biological modifying agents are produced by recombinant DNA technology and they are targeted against the cytokines and certain steps in the intracellular pathway of inflammatory cell receptors on which cytokines act. Biological agents used for treatment of RA are TNFα inhibitors like etanercept, golimumab, adalimumab, certolizumab pegol, infliximab, interleukin-1 receptor antagonist like anakinra and interleukin-6 receptor antagonist like Tozalizumab. The drug rituximab, which is used widely in the treatment of RA patients, is an anti-CD20 B cell depleting monoclonal antibody. Tofacitinib is a biological agent under study that acts against Janus kinases and in turn inhibit growth factors and cytokines acting through this pathway.

There are evidences in support of administration of DMARD's early in the course of RA treatment. This prevents the progression of the disease and thus prevents the deformity and debility caused by the disease.

Assessment And Monitoring

RA patients are to be frequently assessed for disease activity and for any signs of drug toxicity.

Assessment of disease activity

RA patients are to be reviewed every 3-4 months. Patients with severe disease should be seen every 1-month. RA patients should be started on combination

treatment with anti-inflammatory and DMARD's, if there is no remission physician should change the DMARD or add another one so that patient can achieve disease control earlier and prevent the formation of deformity. So there is need for close monitoring of the patient while initiating the therapy and monitoring closely helps pick the patient resistant to therapy earlier, resulting in early change of the treatment regimen.

History regarding improvement in morning stiffness, difficulty in movement of joints, fatigueness, any new joint involvement should be enquired during the follow-up visits. Symptoms suggestive of extra articular manifestation should also be enquired during the follow-up visits.

While examining the patient one should look previously involved joint, whether any new joint shows any signs of inflammation, assess the degree of movement restriction brought about by the joint involvement and any signs suggestive of extra articular manifestation.

Laboratory monitoring

CRP and ESR are the parameters that help in monitoring of the disease activity. Serum albumin and hemoglobin will be reduced in increased disease activity. Platelets should be checked, as increase in the count occurs during ongoing inflammation.

Drug toxicity monitoring is according to ACR recommendations.

People undergoing treatment with glucocorticoids should be monitored for osteoporosis, diabetes and hypertension. Imaging baseline X-ray of the joint should be taken, should be repeated every 2 yearly for osteopenia, joint space reduction and bone erosion. If any of such changes occur, it means that the current drug regimen patient is getting is not sufficient and change to DMARD's or adjustment of dose to be considered.

Strict control of disease

Measures should be taken to control the inflammation and thus disease progression. Starting newly diagnosed cases in combination therapy with DMARD's and anti-inflammatory agents is ideal. The disease activity reduction should be monitored every three months and if there are any signs of disease activity, an additional DMARD should be added or DMARD currently in use should be changed or dose should be escalated.

A person is said to be resistant to initial therapy with DMARD when the patient fails to achieve remission, low disease activity after three to six months of treatment with DMARD in maximum dose in therapeutic range / in addition to DMARD treatment requirement of glucocorticoids in dose more than 7.5mg/d (prednisone)or its equivalent / recurrent disease flares which resulted in treatment with multiple courses of glucocorticoid leading to therapeutic dose which exceeded acceptable dose for chronic therapy.

Treatment for drug resistance

Selection of drugs is based upon the prior treatment, patient choice of route of drug administration, cost of drug, availability of drugs and patient co morbidities.

Patient with mild disease who has been started on treatment with sulfasalazine (SSZ 1000mg twice daily), hydroxychloroquine (HCQ 400mg /day) initially and has not responded to retreatment after 6 months, addition of methotrexate (MTX) is considered.

Patient who was started on MTX initially with dose 25mg/week and not responded after 6 months should be treated with triple regimen (i.e.) HCQ, MTX, -SSZ or MTX with TNFα inhibitors (etanarcept, adalimumab, infliximab). Monotherapy is not recommended in treatment of RA patients. Triple therapy is preferred in people who prefer oral route of administration of medication, mild disease and who consider cost effectiveness.

If patients' symptoms are not improving after addition of TNF α to MTX, then addition of alternative TNF-α inhibitors should be considered.

People should be monitored every fourth weekly whenever there is change of regimen for any clinical improvement and side effects. Close monitoring is required only then we will able to adjust the drugs with out delaying treatment if there is not much of improvement.

If patients are not showing improvement with TNF-α, then drug that acts with different mechanism should be added like abatacept, rituximab and tocilizumab.

People who were started on Triple therapy due to cost consideration or patient preference and not responding to treatment leflunomide should be considered rather than alternative consideration like gold, azathioprine and cyclosporine.

During flare up of disease, intraarticular steroid injection can be given. Oral steroids instead of using NSAIDS alone for control of the inflammatory process should be gradually tapered once new DMARD's are started.

ACR/EULAR criteria for remission

At any time point, patient must satisfy all of the following:

Tender joint count <_ 1

Swollen joint count<_ 1

CRP<_ 1 mg/dl

Patients' global assessment < 1(on a 0-10 scale)

OR

At sometime, patient must have a simplified Disease Activity Index Score of < 3.3

Surgical treatment

It is last resort when patient has not responded properly to medical management leading to severely deformed joints. For large joints like knee, elbow and hip, total arthroplasty can be done. Surgical options for the affected small hand joints are limited. Silicon implants can be used for MCP arthorplasty.

Special treatment consideration

Pregnancy is a condition in which 75% of the women have an improvement of symptoms. Flare up occurs during post partum period. Rarely if flare up happens in pregnancy, it is managed by glucocorticoids; HCQ, SSZ and other drugs such as MTX are contraindicated since there are chances for teratogenicity as per animal studies. Biological agents are not used as the effect of it on the fetus is not studied till date.

Old Age – Drugs used in young and old are essentially the same. After 60yrs of age, GFR tend to decrease so there should be dose adjustment for drugs that are predominantly excreted through kidneys. Drugs like MTX are not prescribed once S.creatinine >2mg/dl.

Materials & Methods

MATERIALS & METHODS

This study was undertaken in patients attending the Out Patient Department (OPD) of Rheumatology, in collaboration with the Department of Neurology in Coimbatore Medical College Hospital, Coimbatore from September 2014 to August 2015. The study was approved by the Institute's ethics committee.

PATIENTS

This study was conducted in 50 cases of rheumatoid arthritis patients attending the rheumatology OPD.

SELECTION CRITERIA

Inclusion Criteria

Patient attending the rheumatology outpatient department (OPD) satisfying the ACR/EULAR criteria 2010 for diagnosis of rheumatoid arthritis were included in this study.

Exclusion Criteria

Minors (below the age of consent)

Patients not capable of giving consent (psychiatric and mentally retarded patients)

Patients not willing to undergo study.

Patients with diabetes mellitus, HIV infection, hypothyroidism, amyloidosis, liver disease, chronic renal failure, malignancy and alcohol intake.

Patients who underwent orthopedic surgery

Table 1: ACR-EULAR CRITERIA (2010) FOR CLASSIFICATION OF RA[90][91]

JOINT INVOLVEMENT	1 large joints (shoulder, knee, hip, ankle, elbow)	0
	2-10 large joints	1
	1-3 small joints (MCP, PIP, Thumb, IP, MTP, wrist)	2
	4-10 small joints	3
	>10 joints (At least 1 small joint)	5
SEROLOGY	Negative RF and Negative ACPA	0
	Low positive RF or Low positive ACPA (>3 times ULN)	2
	High positive RF or High positive ACPA (>3 times ULN)	3
ACUTE PHASE REACTANTS	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
DURATION OF SYMPTOMS	<6 weeks	0
	>6 weeks	1

METHODOLOGY

Study was conducted in 50 consecutive patients with rheumatoid arthritis attending rheumatology OPD fitting the ACR-EULAR 2010 and inclusion criteria. Patients were selected with symptoms of RA of more than 2 years duration. Informed consent was obtained from the patient before start of the study. Detailed history taking and clinical examination was performed in all the selected patients s and were also checked for signs and symptoms of peripheral neuropathy. Laboratory investigations like erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), renal function tests (RFT), liver function tests (LFT), complete blood count (CBC), HIV antibody testing and blood sugar were performed. Patients selected were further subjected to Nerve Conduction Study (NCS) – electrophysiological study.

Nerve conduction Study

Nerve conduction study was performed in the Neurology department, Coimbatore Medical College Hospital. NCS was done bilaterally on both upper and lower limbs. Both motor and sensory nerve conduction parameters were tested.

It was done by peripheral nerve stimulation. Peripheral nerves were activated by placement of stimulating cathode and anode over the nerve, generating an electrical impulse. Duration and strength of stimulus can be adjusted, of which 0.1-0.2 milliseconds was utilized in the study. Greater was the strength of the

stimulus, more the number of nerve fiber were recruited and thus action potential was increased until it reached the maximum. Recording of the electrical activity resulting from nerve excitation was done using surface electrodes.

Electrodes were placed over a distal muscle, sensory nerve or cutaneous nerve distribution. Motor nerve studies were recorded from muscles. In motor nerve conduction studies, compound muscle action potential (CMAP) is recorded. Motor conduction was recorded by orthodromic method. (The stimulus is conducted from nerve to muscle in the direction of physiologic conduction). Sensory nerve conduction can be recorded in either orthodromic or antidromic method. For sensory recording, antidromic method was utilized.

Motor conduction studies

Nerves selected for study in upper limb were ulnar and median and measurement was taken from elbow and wrist. In lower limbs, tibial and peroneal nerves were used for study and electrodes were placed on knee and ankle. Conduction velocities, latency and amplitudes were measured and compared with normal values.

Sensory conduction studies

Nerves studied for sensory conduction studies in upper limb were ulnar and median nerves. Electrode was placed in wrist for measurement. In lower limb,

sural nerve was used and the electrode was placed in mid-calf. Conduction velocities, amplitude, latency were recorded by antidromic method.

The interpretation of electrophysiological parameters (CMAP's, SNAP's and conduction velocity, latency and amplitude) was performed by the consultant neurologist.

Data obtained from the NCS was compared to age, sex, duration of the disease, rheumatoid factor and ESR levels.

Statistical analysis

Chi-square test was used to compare the association between dependent variables and Levene's T test was used to compare the association between independent variables.

All statistical analysis was performed using SPSS software version 22.

All analysis were arrived at 5% level of significance and p value < 0.05 were considered as significant.

Results

RESULTS

A total of 50 patients diagnosed with rheumatoid arthritis based on ACR criteria were recruited for evaluating the prevalence of peripheral neuropathy, during the study period from September 2014 to September 2015 (1 year).

Table 2: Mean age (with standard deviation) of the study population.

Age	Mean	Standard deviation
	49.7	11.9

The age of the study population ranged between 20 – 80 years and the mean age group of the study population was 49.7 years. (Table 2)

Table 3: Sex distribution of the study population.

Sex	Number (n)	Percentage (%)
Male	12	24
Female	38	76
Total	50	100

In the study population, 12 were males (24%), and 38 were females (76%). (Table 3)

Table 4: Frequency of various patterns of axonal neuropathy in the study population

Pattern of axonal neuropathy	Frequency	Number (n)	Percentage (%)
Sensory NCN – UL	Present	13	26
	Absent	37	74
Sensory NCN – LL	Present	-	-
	Absent	50	100
Motor NCN – UL	Present	2	4
	Absent	48	96
Motor NCN – LL	Present	12	24
	Absent	38	76
Mixed NCN – UL	Present	15	30
	Absent	35	70
Mixed NCN – LL	Present	25	50
	Absent	25	50
CTS - CN	Present	2	4
	Absent	48	96

Based on nerve conduction studies, 37 (74%) out of 50 patients had axonal neuropathy. No demyelinating neuropathy pattern was detected in the study population.

Various patterns of axonal neuropathy were observed in the nerve conduction study. Non-compressive neuropathy (NCN) was more prevalent than compressive neuropathy. All 37 patients with axonal neuropathy changes had patterns of non-compressive neuropathy (NCN), whereas only 2 patients were observed to have compressive neuropathy (carpal tunnel syndrome: CTS-CN). Mixed pattern of non-compressive neuropathy affecting the lower limbs was the commonest pattern of axonal neuropathy observed in the study population (50%). (Table 4)

Table 5: Association of axonal changes with various patterns of neuropathy.

Parameter	Frequency	Pattern of neuropathy		P value
Axonal neuropathy		Sensory NCN – UL		
		Present	Absent	
	Present	12	25	0.08
	Absent	0	12	
		Sensory NCN – LL		
		Present	Absent	
	Present	-	37	N.A
	Absent	-	13	
Axonal neuropathy		Motor NCN – UL		
		Present	Absent	
	Present	2	35	0.39
	Absent	0	13	
		Motor NCN – LL		
		Present	Absent	
	Present	12	25	**0.02 ***
	Absent	0	13	
Axonal neuropathy		Mixed NCN – UL		
		Present	Absent	
	Present	15	22	**0.006 ***
	Absent	0	13	
		Mixed NCN – LL		

		Present	Absent	
	Present	25	12	**0.000 #**
	Absent	0	13	
Axonal neuropathy		CTS - CN		
		Present	Absent	
	Present	2	35	0.39
	Absent	0	13	

*** P value ≤ 0.05, hence the association is significant**

 # P value ≤ 0.001, hence the association is extremely significant

Significant association was observed in the occurrence of mixed non-compressive neuropathy pattern of axonal neuropathy in both upper and lower limbs and motor non-compressive neuropathy involving the lower limbs in patients with rheumatoid arthritis. (Table 5)

Table 6: Association between axonal neuropathy and age, duration of rheumatoid arthritis & erythrocyte sedimentation rate (ESR).

Type of neuropathy	Frequency	Mean age (years) ± S.D	Mean duration RA (years) ± S.D	Mean ESR (mm) ± S.D
Axonal neuropathy	Present	50.6 ± 12.6	5.7 ± 3.5	32.0 ± 7.0
	Absent	47.2 ± 9.8	3.4 ± 2.4	33.0 ± 5.4
	P value	0.40	**0.01***	0.49

*** P value ≤ 0.05, hence the association is significant.**

Significant association was observed between the occurrence of axonal neuropathic changes and the duration of RA illness, whereas comparison of mean age of onset of RA and ESR levels between patients with and without peripheral neuropathy (axonal changes) and were found to be statistically insignificant. (Table 6)

Table 7: Frequency of rheumatoid factor in the study population.

Rheumatoid factor	Number (n)	Percentage (%)
Present	20	40
Absent	30	60
Total	50	100

The study population was assessed for the presence of rheumatoid factor and was observed in 40% of RA patients (n= 20). (Table 7) No significant association was observed between sex for the presence of rheumatoid factor in the study population. (Table 8)

Table 8: Association of sex with rheumatoid factor.

Sex	Rheumatoid factor		P value
	No. present (%)	No. absent (%)	
Male	6 (50%)	6 (50%)	0.417
Female	14 (36.8%)	24 (63.2%)	

Table 9: Frequency of axonal neuropathy in relation to rheumatoid factor

Parameter	Frequency	Rheumatoid factor (RF)		P value
Axonal neuropathy		Present	Absent	**0.03 ***
	Present	18	19	
	Absent	2	11	

*** P value ≤ 0.05, hence the association is significant**

The presence of rheumatoid factor in patients with rheumatoid arthritis was observed to have significant association with the occurrence of peripheral neuropathy. (Table 9) The presence of individual patterns of axonal neuropathy changes was compared with the presence of rheumatoid factor and was found to be statistically insignificant. (Table 10).

Table 10: Frequency of various patterns of axonal neuropathy in relation to rheumatoid factor

Parameter	Frequency	Pattern of axonal neuropathy		P value
Rheumatoid factor		Sensory NCN – UL		
		Present	Absent	
	Present	5	15	0.89
	Absent	8	22	
		Sensory NCN – LL		
		Present	Absent	
	Present	-	20	N.A
	Absent	-	30	
Rheumatoid factor		Motor NCN – UL		
		Present	Absent	
	Present	2	18	0.07
	Absent	0	30	
		Motor NCN – LL		
		Present	Absent	
	Present	7	13	0.13
	Absent	5	25	
Rheumatoid factor		Mixed NCN – UL		
		Present	Absent	
	Present	7	13	0.52
	Absent	8	22	

		Mixed NCN – LL		
		Present	Absent	
	Present	11	9	0.56
	Absent	14	16	
Rheumatoid factor		CTS - CN		
		Present	Absent	
	Present	1	19	0.76
	Absent	1	29	

Table 11: Association between rheumatoid factor and patterns of axonal neuropathy among males (n=12).

Parameter	Frequency	Pattern of axonal neuropathy		P value
Rheumatoid factor		Sensory NCN – UL		
		Present	Absent	
	Present	2	4	0.55
	Absent	3	3	
		Sensory NCN – LL		
		Present	Absent	
	Present	-	6	N.A
	Absent	-	6	
Rheumatoid factor		Motor NCN – UL		
		Present	Absent	
	Present	-	6	N.A
	Absent	-	6	
		Motor NCN – LL		
		Present	Absent	
	Present	1	5	0.50
	Absent	2	4	
Rheumatoid factor		Mixed NCN – UL		
		Present	Absent	
	Present	3	3	0.22
	Absent	1	5	

		Mixed NCN – LL		
		Present	Absent	
	Present	5	1	0.22
	Absent	3	3	
Rheumatoid factor		CTS - CN		
		Present	Absent	
	Present	0	6	0.29
	Absent	1	5	

Table 12: Association between rheumatoid factor and patterns of axonal neuropathy among females (n=38).

Parameter	Frequency	Pattern of axonal neuropathy		P value
Rheumatoid factor		Sensory NCN – UL		
		Present	Absent	
	Present	3	11	0.96
	Absent	5	19	
		Sensory NCN – LL		
		Present	Absent	
	Present	-	14	N.A
	Absent	-	24	
Rheumatoid factor		Motor NCN – UL		
		Present	Absent	
	Present	2	12	**0.05 ***
	Absent	0	24	
		Motor NCN – LL		
		Present	Absent	
	Present	6	8	**0.03 ***
	Absent	3	21	
Rheumatoid factor		Mixed NCN – UL		
		Present	Absent	
	Present	4	10	0.96
	Absent	7	17	

		Mixed NCN – LL		
		Present	Absent	
	Present	6	8	0.85
	Absent	11	13	
Rheumatoid factor		CTS - CN		
		Present	Absent	
	Present	1	23	0.43
	Absent	0	14	

*** P value ≤ 0.05, hence the association is significant**

Association of rheumatoid factor with various patterns of axonal neuropathy was compared between males and females and significant prediction was observed for non-compressive neuropathy of both upper and lower limbs in females. (Table 11 and 12)

Table 13: Association between patterns of axonal neuropathy and age of the patients

	Pattern of axonal neuropathy	Frequency	Mean age (years) ± S.D	P value
Age at detection of neuropathy	Sensory NCN – UL	Present	49 ± 16	0.06
		Absent	50 ± 10	
	Sensory NCN – LL	Present	-	N.A
		Absent	50 ± 12	
	Motor NCN – UL	Present	43 ± 7	0.41
		Absent	50 ± 12	
	Motor NCN – LL	Present	47 ± 17	0.10
		Absent	50 ± 10	
	Mixed NCN – UL	Present	54 ± 10	0.13
		Absent	48 ± 12	
	Mixed NCN – LL	Present	52 ± 10	0.31
		Absent	47 ± 13	
	CTS - CN	Present	58 ± 3	0.17
		Absent	49 ± 12	

Table 14: Frequency of various patterns of axonal neuropathy in relation to sex of the patient.

Parameter	Frequency	Pattern of axonal neuropathy		P value
Sex		Sensory NCN – UL		
		Present	Absent	
	Male	5	7	0.15
	Female	8	30	
		Sensory NCN – LL		
		Present	Absent	
	Male	-	12	N.A
	Female	-	38	
Sex		Motor NCN – UL		
		Present	Absent	
	Male	0	12	0.41
	Female	2	36	
		Motor NCN – LL		
		Present	Absent	
	Male	3	9	0.92
	Female	9	29	
Sex		Mixed NCN – UL		
		Present	Absent	
	Male	4	8	0.77
	Female	11	27	

		Mixed NCN – LL		
		Present	Absent	
	Male	8	4	0.18
	Female	17	21	
Sex		CTS - CN		
		Present	Absent	
	Male	1	11	0.38
	Female	1	37	

The mean age of detection of neuropathy, sex, mean duration since diagnosis of RA and mean ESR levels were compared between patients with and without various patterns of peripheral neuropathy (axonal changes) and were found to be statistically insignificant association between the variables. (Table 13, 14, 15 & 16)

Table 15: Association between patterns of axonal neuropathy and duration of rheumatoid arthritis.

	Pattern of axonal neuropathy	Frequency	Mean duration (years) ± S.D	P value
Duration since diagnosis of rheumatoid arthritis	Sensory NCN – UL	Present	5.77 ± 3.6	0.86
		Absent	5.51 ± 3.2	
	Sensory NCN – LL	Present	N.A	N.A
		Absent	5.58 ± 3.2	
	Motor NCN – UL	Present	12.5 ± 3.5	0.94
		Absent	5.29 ± 2.9	
	Motor NCN – LL	Present	5.92 ± 4.0	0.23
		Absent	5.47 ± 3.0	
	Mixed NCN – UL	Present	5.27 ± 3.0	0.82
		Absent	5.71 ± 3.4	
	Mixed NCN – LL	Present	5.64 ± 3.4	0.68
		Absent	5.52 ± 3.2	
	CTS - CN	Present	4.00 ± 1.4	0.21
		Absent	5.65 ± 3.3	

Table 16: Association between patterns of axonal neuropathy and erythrocyte sedimentation rate (ESR in mm).

	Pattern of axonal neuropathy	Frequency	Mean ESR (mm) ± S.D	P value
Erythrocyte sedimentation rate (ESR)	Sensory NCN – UL	Present	32 ± 7.9	0.42
		Absent	32.3 ± 6.2	
	Sensory NCN – LL	Present	N.A	N.A
		Absent	32.2 ± 6.6	
	Motor NCN – UL	Present	28.5 ± 2.1	0.20
		Absent	32.7 ± 6.7	
	Motor NCN – LL	Present	31.8 ± 6.0	0.41
Erythrocyte sedimentation rate (ESR)		Absent	32.4 ± 6.9	
	Mixed NCN – UL	Present	31.2 ± 6.9	0.86
		Absent	32.7 ± 6.5	
	Mixed NCN – LL	Present	32.1 ± 7.6	0.26
		Absent	32.4 ± 5.6	
	CTS - CN	Present	32.5 ± 4.9	0.54
		Absent	32.2 ± 6.7	

Table 17: Association between peripheral neuropathy symptoms with age and duration of illness.

Parameter	Frequency	Mean age (years) ± S.D	Mean illness duration (years) ± S.D
Peripheral neuropathy symptoms	Present	58 ± 7	5.1 ± 2.8
	Absent	49 ± 13	3.6 ± 3.4
	P value	0.09	**0.03 ***

*** P value ≤ 0.05, hence the association is significant**

Significant association was observed between the duration of RA illness and occurrence of peripheral neuropathy symptoms, whereas no significant association was observed in comparison of mean age, sex, and mean ESR levels between patients with and without symptoms of peripheral neuropathy (axonal changes). (Table 17, 18, 19 & 20)

Table 18: Association between peripheral neuropathy symptoms with sex.

Parameter	Frequency	Sex		P value
Peripheral neuropathy symptoms		Male	Female	0.74
	Present	18	19	
	Absent	2	11	

Table 19: Association between peripheral neuropathy symptoms with rheumatoid factor.

Parameter	Frequency	Rheumatoid factor		P value
Peripheral neuropathy symptoms		Present	Absent	1.00
	Present	4	6	
	Absent	16	24	

Table 20: Frequency and association of neuropathy symptoms with various patterns of axonal neuropathy.

Parameter	Frequency	Pattern of axonal neuropathy		P value
Peripheral neuropathy symptoms		Sensory NCN – UL		
		Present	Absent	
	Present	0	10	**0.03 ***
	Absent	13	27	
		Sensory NCN – LL		
		Present	Absent	
	Present	-	10	N.A
	Absent	-	40	
Peripheral neuropathy symptoms		Motor NCN – UL		
		Present	Absent	
	Present	1	9	0.28
	Absent	1	39	
		Motor NCN – LL		
		Present	Absent	
	Present	1	9	0.24
	Absent	11	29	
Peripheral neuropathy symptoms		Mixed NCN – UL		
		Present	Absent	
	Present	5	5	0.12
	Absent	10	30	

		Mixed NCN – LL		
		Present	Absent	
	Present	6	4	0.48
	Absent	19	21	
Peripheral neuropathy symptoms		CTS - CN		
		Present	Absent	
	Present	0	10	0.47
	Absent	2	38	

*** P value ≤ 0.05, hence the association is significant**

Significant association was observed in sensory non-compressive neuropathy of upper limbs manifesting with peripheral neuropathy symptoms. (Table 20)

Discussion

DISCUSSION

The study was conducted in 50 RA patients attending the rheumatology OPD in Coimbatore medical college hospital. Among the 50 patients, 12 were males (24%) and 38 were females (76%). The female to male ratio in our study was 3:1,which is similar to findings reported by Wolfe AM *et al*. (1968)[1] There are various other studies that report similar figures that women are more vulnerable to RA than men. This difference can be due to the genetic and hormonal difference where estrogen is found to have a role in causation as it increases immunogenicity.

In our study, the age of the study population was between 20-80 years and the mean age of the study population falls in the 5th decade (49.7yrs) as similarly reported by Gabriel *et al.* (2010).[9] Recently, there is a shift in the RA incidence to older age group. As the age of onset is delayed, the chances for development of complications are also increased.

The prevalence of peripheral neuropathy among RA patients in our study is 74% which is similar to the study conducted by Lanzillo B *et al*. (1998)[101] and Endtz L J *et al.* (1983).[102] In an Indian study conducted in Rohtak, Haryana, by Geethanjali *et al*[103]. an incidence as high as 84% was reported. On the contrary, studies conducted by Monodeep Biswas *et al.* (2011)[104] and Aneja *et al.* (2007) reported the prevalence of neuropathy in RA patients as 39.19% and 37.87%

respectively. Prevalence varies widely among the reported studies and is difficult to compare as each studies have different inclusion and exclusion criteria.

All RA patients with peripheral neuropathy in our study had axonal type of neuropathy and no demyelination type of neuropathy observed. Non-compressive neuropathy was the most common type of axonal neuropathy in our study (74%). Among the axonal neuropathy patterns, mixed sensory motor neuropathy affecting the lower limbs (50%) was the most common type of neuropathy recorded in our study, followed by the pure sensory neuropathy of upper limbs (26%). Other studies conducted by Lanzillo *et al.* (1998), Yazdchi *et al*[105]., and Agarwal *et al*. (2008),[106] also reported mixed sensory motor neuropathy as most common type of neuropathy type in RA patients. As against our study, sensory neuropathy was found to be common in reports of Albani *et al*. (2006),[107] and Monodeep Biswas *et al.,*(2011). In our study, 2 people (4%) were found to have Carpel tunnel Syndrome that was similar to the studies reported by Monodeep Biswas *et al.* (2011) and a Turkish study by Aktekin *et al.* (2008). As regard to the occurrence of CTS various studies show varying percentage ranging between 4%-54.6%[106][108][101].

In our study, no association was found between the age of onset and the occurrence of peripheral neuropathy in RA patients. No gender predilection was also found in the development of neuropathy changes in RA patients. There was no correlation found between ESR levels and development of neuropathic

changes. Significant association was observed between the duration of RA illness and the occurrence of axonal neuropathic changes. Our study findings were in agreement with the findings of Mi Kyung Sim *et al*.[109] and Salih *et al.* (1996).[110]In our study, the type of neuropathy was compared with various parameters like age, sex, duration of the disease, ESR, and no positive correlation was observed between them.

The prevalence of RF positivity in RA patients were 40% and the rest 60% were seronegative. This result questions the use of RF as a diagnostic marker for RA. This finding agrees with the study of Shmerling *et al.,* [111] and Thomas *et al*[112].From our study we could not make out any association between sex and RF positivity. Significance was found between rheumatoid factor (RF) positivity and peripheral neuropathy which was similar to the study findings of Monodeep Biswas *et al (2011).,* and Albani *et al*. (2006).[107] No association was found between RF positivity with any pattern of neuropathy.

In our study, symptoms of peripheral neuropathy like pins and needle sensation, numbness were present in 27% of the RA patients with neuropathic changes. Rest of the 73% of RA patients with neuropathy was asymptomatic. Lanzillo *et al*. (1998) reported a similar figure in relation to the percentage of RA patients with neuropathy presenting with symptoms of peripheral neuropathy.

Correlation between the occurrence of symptoms and sensory neuropathy of upper limb had statistical significance in our study. Significant association was observed between the duration of RA illness and the occurrence of symptoms of peripheral neuropathy. Similar association has been reported by other studies[104][113][114]. In our study, the occurrence of peripheral neuropathy symptoms was seen in RA patients with the mean duration of illness of more than 3.4 years. There was no significant association seen between symptoms of neuropathy and age, or with duration of the disease and also no correlation was found with sex of the patient and development of neuropathy.

Summary

SUMMARY

The study was conducted in 50 RA patients attending rheumatology OPD in Coimbatore Medical college Hospital in collaboration with the neurology department to study the prevalence, type of peripheral neuropathy in RA patient. The study was conducted over a period of 1 year (September 2014 to August 2015).

The age of the study population ranged between 20 – 80 years and the mean age group of the study population was 49.7 years.

In the study population, 12 were males (24%), and 38 were females (76%).

The prevalence of peripheral neuropathy was found to be in 74 % in RA patients. Based on nerve conduction studies, 37 (74%) out of 50 patients had axonal neuropathy.

Non-compressive neuropathy (NCN) was more prevalent (74%) than compressive neuropathy (4%).

Mixed pattern of non-compressive neuropathy affecting the lower limbs was the commonest pattern of axonal neuropathy observed in the study population (50%).

Significant association was observed in the occurrence of mixed non-compressive neuropathy pattern of axonal neuropathy in both upper and lower limbs and motor non-compressive neuropathy involving the lower limbs in patients with rheumatoid arthritis.

Positive correlation was observed between RF positivity and peripheral neuropathy.

In our study, 73 % of the RA patients with neuropathy had no symptoms of peripheral neuropathy. The occurrence of peripheral neuropathy symptoms was seen in RA patients with a mean duration of illness of more than 3.4 years. Significant association was observed between the duration of RA illness and the occurrence of symptoms of peripheral neuropathy.

Conclusion

CONCLUSION

Subclinical peripheral neuropathy is very common in RA patients. Nerve conduction studies (NCS) can detect peripheral neuropathy and differentiate the various patterns of neuropathy. Hence nerve conduction studies (NCS) should be made a mandatory investigation to all RA patients for follow-up visits in order to detect the neuropathic changes early, thus preventing development of debilitating comorbidities by taking appropriate early measures.

References

REFERENCES

1. Wolfe AM, Kellgren JH, Masi AT. The epidemiology of rheumatoid arthritis: a review. II. Incidence and diagnostic criteria. Bull Rheum Dis 1968;19(3):524–9.

2. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29(1):62–7.

3. Zlatanović G, Veselinović D, Cekić S, Zivković M, Dorđević-Jocić J, Zlatanović M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. Bosn J Basic Med Sci Udruženje Basičnih Med Znan Assoc Basic Med Sci 2010;10(4):323–7.

4. Sarzi-Puttini P, Atzeni F, Gerli R, Bartoloni E, Doria A, Barskova T, et al. Cardiac involvement in systemic rheumatic diseases: An update. Autoimmun Rev 2010;9(12):849–52.

5. Johnson RL, Smyth CJ, Holt GW, Lubchenco A, Valentine E. Steroid therapy and vascular lesions in rheumatoid arthritis. Arthritis Rheum 1959;2(3):224–9.

6. Good AE, Christopher RP, Koepke GH, Bender LF, Tarter ME. Peripheral Neuropathy Associated With Rheumatoid Arthritis. A

Clinical And Electrodiagnostic Study Of 70 Consecutive Rheumatoid Arthritis Patients. Ann Intern Med 1965;63:87–99.

7. Nadkar MY, Agarwal R, Samant RS, Chhugani SJ, Idgunji SS, Iyer S, et al. Neuropathy in rheumatoid arthritis. J Assoc Physicians India 2001;49:217–20.

8. Haslock DI, Wright V, Harriman DG. Neuromuscular disorders in rheumatoid arthritis. A motor-point muscle biopsy study. Q J Med 1970;39(155):335–58.

9. Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J Autoimmun 2010;35(1):10–4.

10. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30(11):1205–13.

11. Mandl LA, Costenbader KH, Simard JF, Karlson EW. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. Ann Rheum Dis 2009;68(4):514–8.

12. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365(23):2205–19.

13. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum 2000;43(1):30–7.

14. Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AHM, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. Am J Hum Genet 2007;80(5):867–75.

15. Vincent C, de Keyser F, Masson-Bessière C, Sebbag M, Veys EM, Serre G. Anti-perinuclear factor compared with the so called “antikeratin” antibodies and antibodies to human epidermis filaggrin, in the diagnosis of arthritides. Ann Rheum Dis 1999;58(1):42–8.

16. De Rycke L, Peene I, Hoffman IEA, Kruithof E, Union A, Meheus L, et al. Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Ann Rheum Dis 2004;63(12):1587–93.

17. Auger I, Roudier J. A function for the QKRAA amino acid motif: mediating binding of DnaJ to DnaK. Implications for the association of rheumatoid arthritis with HLA-DR4. J Clin Invest 1997;99(8):1818–22.

18. Kamphuis S, Kuis W, de Jager W, Teklenburg G, Massa M, Gordon G, et al. Tolerogenic immune responses to novel T-cell epitopes

from heat-shock protein 60 in juvenile idiopathic arthritis. Lancet Lond Engl 2005;366(9479):50–6.

19. Wegner N, Wait R, Sroka A, Eick S, Nguyen K-A, Lundberg K, et al. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum 2010;62(9):2662–72.

20. Capellino S, Cosentino M, Wolff C, Schmidt M, Grifka J, Straub RH. Catecholamine-producing cells in the synovial tissue during arthritis: modulation of sympathetic neurotransmitters as new therapeutic target. Ann Rheum Dis 2010;69(10):1853–60.

21. Szekanecz Z, Pakozdi A, Szentpetery A, Besenyei T, Koch AE. Chemokines and angiogenesis in rheumatoid arthritis. Front Biosci Elite Ed 2009;1:44–51.

22. Polzer K, Baeten D, Soleiman A, Distler J, Gerlag DM, Tak PP, et al. Tumour necrosis factor blockade increases lymphangiogenesis in murine and human arthritic joints. Ann Rheum Dis 2008;67(11):1610–6.

23. Lebre MC, Jongbloed SL, Tas SW, Smeets TJM, McInnes IB, Tak PP. Rheumatoid arthritis synovium contains two subsets of CD83-DC-LAMP- dendritic cells with distinct cytokine profiles. Am J Pathol 2008;172(4):940–50.

24. Schröder AE, Greiner A, Seyfert C, Berek C. Differentiation of B cells in the nonlymphoid tissue of the synovial membrane of patients with rheumatoid arthritis. Proc Natl Acad Sci U S A 1996;93(1):221–5.

25. Chabaud M, Fossiez F, Taupin JL, Miossec P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. J Immunol Baltim Md 1950 1998;161(1):409–14.

26. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med 2009;361(9):888–98.

27. Nadkarni S, Mauri C, Ehrenstein MR. Anti-TNF-alpha therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF-beta. J Exp Med 2007;204(1):33–9.

28. Genovese MC, Van den Bosch F, Roberson SA, Bojin S, Biagini IM, Ryan P, et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum 2010;62(4):929–39.

29. Edwards JCW, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350(25):2572–81.

30. Seibl R, Birchler T, Loeliger S, Hossle JP, Gay RE, Saurenmann T, et al. Expression and regulation of Toll-like receptor 2 in rheumatoid arthritis synovium. Am J Pathol 2003;162(4):1221–7.

31. Cascão R, Rosário HS, Souto-Carneiro MM, Fonseca JE. Neutrophils in rheumatoid arthritis: More than simple final effectors. Autoimmun Rev 2010;9(8):531–5.

32. Nigrovic PA, Lee DM. Synovial mast cells: role in acute and chronic arthritis. Immunol Rev 2007;217:19–37.

33. Hueber AJ, Asquith DL, Miller AM, Reilly J, Kerr S, Leipe J, et al. Mast cells express IL-17A in rheumatoid arthritis synovium. J Immunol Baltim Md 1950 2010;184(7):3336–40.

34. Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. Cell 1996;85(3):307–10.

35. Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, et al. Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A 2011;108(9):3731–6.

36. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007;7(6):429–42.

37. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. J Clin Invest 2008;118(11):3537–45.

38. Bradfield PF, Amft N, Vernon-Wilson E, Exley AE, Parsonage G, Rainger GE, et al. Rheumatoid fibroblast-like synoviocytes overexpress the chemokine stromal cell-derived factor 1 (CXCL12), which supports distinct patterns and rates of CD4+ and CD8+ T cell migration within synovial tissue. Arthritis Rheum 2003;48(9):2472–82.

39. Filer A, Parsonage G, Smith E, Osborne C, Thomas AMC, Curnow SJ, et al. Differential survival of leukocyte subsets mediated by synovial, bone marrow, and skin fibroblasts: site-specific versus activation-dependent survival of T cells and neutrophils. Arthritis Rheum 2006;54(7):2096–108.

40. Aupperle KR, Boyle DL, Hendrix M, Seftor EA, Zvaifler NJ, Barbosa M, et al. Regulation of synoviocyte proliferation, apoptosis, and invasion by the p53 tumor suppressor gene. Am J Pathol 1998;152(4):1091–8.

41. Schett G, Redlich K, Xu Q, Bizan P, Gröger M, Tohidast-Akrad M, et al. Enhanced expression of heat shock protein 70 (hsp70) and heat shock factor 1 (HSF1) activation in rheumatoid arthritis synovial tissue. Differential regulation of hsp70 expression and hsf1 activation in synovial fibroblasts by proinflammatory cytokines, shear stress, and antiinflammatory drugs. J Clin Invest 1998;102(2):302–11.

42. Amano T, Yamasaki S, Yagishita N, Tsuchimochi K, Shin H, Kawahara K, et al. Synoviolin/Hrd1, an E3 ubiquitin ligase, as a novel pathogenic factor for arthropathy. Genes Dev 2003;17(19):2436–49.

43. Rhee DK, Marcelino J, Baker M, Gong Y, Smits P, Lefebvre V, et al. The secreted glycoprotein lubricin protects cartilage surfaces and inhibits synovial cell overgrowth. J Clin Invest 2005;115(3):622–31.

44. Van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. Br J Rheumatol 1995;34 Suppl 2:74–8.

45. Schett G, Teitelbaum SL. Osteoclasts and arthritis. J Bone Miner Res Off J Am Soc Bone Miner Res 2009;24(7):1142–6.

46. Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13(2):156–63.

47. Jimenez-Boj E, Redlich K, Türk B, Hanslik-Schnabel B, Wanivenhaus A, Chott A, et al. Interaction between synovial inflammatory tissue and bone marrow in rheumatoid arthritis. J Immunol Baltim Md 1950 2005;175(4):2579–88.

48. Prete M, Racanelli V, Digiglio L, Vacca A, Dammacco F, Perosa F. Extra-articular manifestations of rheumatoid arthritis: An update. Autoimmun Rev 2011;11(2):123–31.

49. Melchers I, Blaschke S, Hecker M, Cattaruzza M. The -786C/T single-nucleotide polymorphism in the promoter of the gene for endothelial nitric oxide synthase: insensitivity to physiologic stimuli as a risk factor for rheumatoid arthritis. Arthritis Rheum 2006;54(10):3144–51.

50. Genta MS, Genta RM, Gabay C. Systemic rheumatoid vasculitis: a review. Semin Arthritis Rheum 2006;36(2):88–98.

51. Sayah A, English JC. Rheumatoid arthritis: a review of the cutaneous manifestations. J Am Acad Dermatol 2005;53(2):191–209; quiz 210–2.

52. Mattey DL, Dawes PT, Fisher J, Brownfield A, Thomson W, Hajeer AH, et al. Nodular disease in rheumatoid arthritis: association with cigarette smoking and HLA-DRB1/TNF gene interaction. J Rheumatol 2002;29(11):2313–8.

53. Kato H, Yamakawa M, Ogino T. Complement mediated vascular endothelial injury in rheumatoid nodules: a histopathological and immunohistochemical study. J Rheumatol 2000;27(8):1839–47.

54. Saraux A, Allain J, Guedes C, Baron D, Youinou P, Le Goff P. Raynaud's phenomenon in rheumatoid arthritis. Br J Rheumatol 1996;35(8):752–4.

55. Tansey RJ, Wragg EA, Herrick AL. Raynaud's phenomenon and hand function in patients with rheumatoid arthritis. J Rheumatol 2010;37(6):1358–9.

56. Pope JE, Al-Bishri J, Al-Azem H, Ouimet JM. The temporal relationship of Raynaud's phenomenon and features of connective tissue disease in rheumatoid arthritis. J Rheumatol 2008;35(12):2329–33.

57. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatol Oxf Engl 2010;49(8):1483–9.

58. Lioté H. [Pulmonary manifestation of rheumatoid arthritis]. Rev Mal Respir 2008;25(8):973–88.

59. Antoniou KM, Mamoulaki M, Malagari K, Kritikos HD, Bouros D, Siafakas NM, et al. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. Clin Exp Rheumatol 2007;25(1):23–8.

60. Nurmohamed MT. Cardiovascular risk in rheumatoid arthritis. Autoimmun Rev 2009;8(8):663–7.

61. Turiel M, Sitia S, Atzeni F, Tomasoni L, Gianturco L, Giuffrida M, et al. The heart in rheumatoid arthritis. Autoimmun Rev 2010;9(6):414–8.

62. Gerli R, Bartoloni Bocci E, Sherer Y, Vaudo G, Moscatelli S, Shoenfeld Y. Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis. Ann Rheum Dis 2008;67(5):724–5.

63. Weng N-P, Akbar AN, Goronzy J. CD28(-) T cells: their role in the age-associated decline of immune function. Trends Immunol 2009;30(7):306–12.

64. Gerli R, Vaudo G, Bocci EB, Schillaci G, Bistoni O, Shoenfeld Y. Different roles for anti-cyclic citrullinated peptide antibodies and CD4+CD28null cells in the acceleration of atherosclerosis in rheumatoid arthritis: comment on the article by Farragher et al. Arthritis Rheum 2009;60(2):631–2.

65. Korpela M, Mustonen J, Teppo AM, Helin H, Pasternack A. Mesangial glomerulonephritis as an extra-articular manifestation of rheumatoid arthritis. Br J Rheumatol 1997;36(11):1189–95.

66. Moriguchi M, Terai C, Koseki Y, Uesato M, Nakajima A, Inada S, et al. Influence of genotypes at SAA1 and SAA2 loci on the development and the length of latent period of secondary AA-amyloidosis in patients with rheumatoid arthritis. Hum Genet 1999;105(4):360–6.

67. Kindy MS, de Beer MC, Yu J, de Beer FC. Expression of mouse acute-phase (SAA1.1) and constitutive (SAA4) serum amyloid A

isotypes: influence on lipoprotein profiles. Arterioscler Thromb Vasc Biol 2000;20(6):1543–50.

68. Nakamura T. Clinical strategies for amyloid A amyloidosis secondary to rheumatoid arthritis. Mod Rheumatol Jpn Rheum Assoc 2008;18(2):109–18.

69. Wu C-C, Yu H-C, Yen J-H, Tsai W-C, Liu H-W. Rare extra-articular manifestation of rheumatoid arthritis: scleromalacia perforans. Kaohsiung J Med Sci 2005;21(5):233–5.

70. Atchia II, Kidd CE, Bell RWD. Rheumatoid arthritis-associated necrotizing scleritis and peripheral ulcerative keratitis treated successfully with infliximab. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis 2006;12(6):291–3.

71. Balint GP, Balint PV. Felty's syndrome. Best Pract Res Clin Rheumatol 2004;18(5):631–45.

72. Newman KA, Akhtari M. Management of autoimmune neutropenia in Felty's syndrome and systemic lupus erythematosus. Autoimmun Rev 2011;10(7):432–7.

73. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59(12):1690–7.

74. Watson P, Fekete J, Deck J. Central nervous system vasculitis in rheumatoid arthritis. Can J Neurol Sci J Can Sci Neurol 1977;4(4):269–72.

75. MD RBD, MD GMF, MD JJ, PhD JCMM. Bradley's Neurology in Clinical Practice, 2-Volume Set: Expert Consult - Online and Print, 6e. 6 edition. Philadelphia, PA: Saunders; 2012.

76. Herbison GJ, Teng C, Martin JH, Ditunno JF. Carpal tunnel syndrome in rheumatoid arthritis. Am J Phys Med 1973;52(2):68–74.

77. Barnes CG, Currey HL. Carpal tunnel syndrome in rheumatoid arthritis. A clinical and electrodiagnostic survey. Ann Rheum Dis 1967;26(3):226–33.

78. Chamberlain MA, Corbett M. Carpal tunnel syndrome in early rheumatoid arthritis. Ann Rheum Dis 1970;29(2):149–52.

79. Fleming A, Dodman S, Crown JM, Corbett M. Extra-articular features in early rheumatoid disease. Br Med J 1976;1(6020):1241–3.

80. Baylan SP, Paik SW, Barnert AL, Ko KH, Yu J, Persellin RH. Prevalence of the tarsal tunnel syndrome in rheumatoid arthritis. Rheumatol Rehabil 1981;20(3):148–50.

81. Brick JE, Brick JF. Neurologic manifestations of rheumatologic disease. Neurol Clin 1989;7(3):629–39.

82. Pallis CA, Scott JT. PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS. Br Med J 1965;1(5443):1141–7.

83. Ferguson RH, Slocumb CH. Peripheral neuropathy in rheumatoid arthritis. Bull Rheum Dis 1961;11:251–4.

84. White SH, Goodfellow JW, Mowat A. Posterior interosseous nerve palsy in rheumatoid arthritis. J Bone Joint Surg Br 1988;70(3):468–71.

85. Weller RO, Bruckner FE, Chamberlain MA. Rheumatoid neuropathy: a histological and electrophysiological study. J Neurol Neurosurg Psychiatry 1970;33(5):592–604.

86. Whiting PF, Smidt N, Sterne JAC, Harbord R, Burton A, Burke M, et al. Systematic review: accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med 2010;152(7):456–64; W155–66.

87. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146(11):797–808.

88. Finckh A, Liang MH. Anti-cyclic citrullinated peptide antibodies in the diagnosis of rheumatoid arthritis: bayes clears the haze. Ann Intern Med 2007;146(11):816–7.

89. Lee DM, Schur PH. Clinical utility of the anti-CCP assay in patients with rheumatic diseases. Ann Rheum Dis 2003;62(9):870–4.

90. Pincus T, Callahan LF. How many types of patients meet classification criteria for rheumatoid arthritis? J Rheumatol 1994;21(8):1385–9.

91. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315–24.

92. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580–8.

93. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569–81.

94. Suhrbier A, La Linn M. Clinical and pathologic aspects of arthritis due to Ross River virus and other alphaviruses. Curr Opin Rheumatol 2004;16(4):374–9.

95. Toivanen A. Alphaviruses: an emerging cause of arthritis? Curr Opin Rheumatol 2008;20(4):486–90.

96. Smith CA, Petty RE, Tingle AJ. Rubella virus and arthritis. Rheum Dis Clin North Am 1987;13(2):265–74.

97. Smith CA, Woolf AD, Lenci M. Parvoviruses: infections and arthropathies. Rheum Dis Clin North Am 1987;13(2):249–63.

98. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3(1):55–78.

99. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatol Oxf Engl 2012;51 Suppl 6:vi5–9.

100. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73(3):492–509.

101. Lanzillo B, Pappone N, Crisci C, di Girolamo C, Massini R, Caruso G. Subclinical peripheral nerve involvement in patients with rheumatoid arthritis. Arthritis Rheum 1998;41(7):1196–202.

102. Endtz LJ, Frenay J, Goor C. Vasculitic neuropathy in RA. Neurology 1983;33(12):1635–6.

103. Geethanjali Sharma, Sood S, R Handa, Singh H. Pulse wave velocity and electroneurophysiological evaluation in patients of rheumatoid arthritis. internet journal of medicalupdate 2011;6(2):15–9.

104. Biswas M, Chatterjee A, Ghosh SK, Dasgupta S, Ghosh K, Ganguly PK. Prevalence, types, clinical associations, and determinants of peripheral neuropathy in rheumatoid patients. Ann Indian Acad Neurol 2011;14(3):194–7.

105. M Y, Ebrahim AA, H M. The electrophysiological evaluation of 70 iranian rheumatoid arthritis patientJ Neuol Sci.(Turkish)2007:24(3):190-6. J Neurol Sci (Turkish) 2007;24(3):190–6.

106. Agarwal V, Singh R, Wiclaf null, Chauhan S, Tahlan A, Ahuja CK, et al. A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. Clin Rheumatol 2008;27(7):841–4.

107. Albani G, Ravaglia S, Cavagna L, Caporali R, Montecucco C, Mauro A. Clinical and electrophysiological evaluation of peripheral neuropathy in rheumatoid arthritis. J Peripher Nerv Syst JPNS 2006;11(2):174–5.

108. Sivri A, Güler-Uysal F. The electroneurophysiological findings in rheumatoid arthritis patients. Electromyogr Clin Neurophysiol 1999;39(7):387–91.

109. Sim MK, Kim D-Y, Yoon J, Park DH, Kim Y-G. Assessment of peripheral neuropathy in patients with rheumatoid arthritis who complain of neurologic symptoms. Ann Rehabil Med 2014;38(2):249–55.

110. Salih AM, Nixon NB, Gagan RM, Heath P, Hawkins CP, Dawes PT, et al. Anti-ganglioside antibodies in patients with rheumatoid arthritis complicated by peripheral neuropathy. Br J Rheumatol 1996;35(8):725–31.

111. Shmerling RH, Delbanco TL. The rheumatoid factor: an analysis of clinical utility. Am J Med 1991;91(5):528–34.

112. Thomas MJ, Adebajo A, Chapel HM, Webley M. The use of rheumatoid factors in clinical practice. Postgrad Med J 1995;71(841):674–7.

113. Hamed SA, Hamed EA, Elattar AM, Rahman MSA, Amine NF. Cranial and peripheral neuropathy in rheumatoid arthritis with special emphasis to II, V, VII and XI cranial nerves. Aplar J Rheum. 2006;9:216–26.

114. Singh G, Prabhakar S, Kanwar J, Deodhar SD, Sehgal S. Peripheral neuropathy due to rheumatoid vasculitis: A clinical neuro-electrophysiological and histological case study. Neurology India. 1996;44:85–7.

Annexures

Proforma

COIMBATORE MEDICAL COLLEGE HOSPITAL

DEPARTEMENT OF RHEUMATOLOGY

NAME:

AGE:

SEX:

OCCUPATION:

DURATION OF ILLNESS:

ANY SYMPTOMS SUGGESTIVE OF PERIPHERAL NEUROPATHY:

PERSONAL H/O: Smoking or Alcoholism

PAST H/O : Diabetes/Hypertension/CAHD/Previous orthopaedic surgery/Malignancy/HIV

CLINICAL EXAMINATION:

INVESTIGATIONS

Complete Haemogram

Haemoglobin- TotalCount- Platelets-

Erythrocyte sedimentation rate

Rheumatoid Factor-

C-Reactive protein

Renal function test

Liver Function Test-

COIMBATORE MEDICAL COLLEGE HOSPITAL
DEPARTMENT OF NEUROLOGY

0 Cms/0 Kg
Date: 22-Aug-2015

Motor Nerve Studies

UPPER LIMB

Nerve: Rt- Median

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Wrist	3.75	13.33	14.9 mV	62.15
2:Elbow	7.29	13.96	14.3 mV	

Nerve: Lt- Median

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Wrist	2.92	11.04	17.7 mV	63.19
2:Elbow	6.56	11.35	16.9 mV	

Nerve: Rt- Ulnar

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Wrist	2.08	11.88	9.2 mV	61.43
2:Elbow	6.15	11.56	8.8 mV	

Nerve: Lt- Ulnar

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Wrist	1.98	12.19	9.9 mV	64.94
2:Elbow	5.83	12.29	8.8 mV	

LOWER LIMB

Nerve: Rt- Peroneal

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Ankle	2.19	13.23	5.8 mV	50.07
2:Knee	9.58	12.19	4.1 mV	

Nerve: Lt- Peroneal

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Ankle	2.34	13.43	6.3 mV	52.09
2:Knee	9.42	12.34	3.9 mV	

Nerve: Lt- Tibial

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Ankle	4.27	8.44	17.9 mV	43.50
2:Knee	11.56	8.23	3.3 mV	

Nerve: Lt- Tibial

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Ankle	4.32	8.32	15.3 mV	42.30
2:Knee	11.43	8.14	3.9 mV	

Sensory Nerve Studies

UPPER LIMB

Nerve: Lt- ALL SNC

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:RT MED Wt	2.92	1.71	42.6 µV	44.52
2:RT ULN Wt	2.00	1.21	77.5 µV	55.00
3:LT MED Wt	2.46	1.38	72.4 µV	52.85
4:LT ULN Wt	2.04	1.33	93.9 µV	53.92

LOWER LIMB

Nerve: Rt- Sural

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Mid Calf	2.34	1.09	6.9 µV	61.24

Nerve: Lt- Sural

Site	Lat1 (mS)	Dur (mS)	Amp	NCV (m/S)
1:Mid Calf	2.21	1.04	7.1 µV	63.35

F Wave Studies

LOWER LIMB

Nerve: Rt- Median

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
4.2 mS	25.6 mS	34.0 mS	29.8 mS

Nerve: Lt- Median

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
2.7 mS	24.4 mS	33.5 mS	29.0 mS

Nerve: Rt- Ulnar

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
2.7 mS	23.3 mS	32.7 mS	28.0 mS

Nerve: Lt- Ulnar

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
2.3 mS	25.6 mS	32.7 mS	29.2 mS

Nerve: Rt- Peroneal Nerve

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
2.1 mS	44.8 mS	48.8 mS	46.8 mS

Nerve: Lt- Peroneal Nerve

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
2.5 mS	41.2 mS	44.5 mS	45.9 mS

Nerve: Rt- Tibial Nerve

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
4.9 mS	42.4 mS	53.7 mS	50.1 mS

Nerve: Lt- Tibial Nerve

M Lat	Fmin Lat	Fmax Lat	Fmean Lat
4.6 mS	44.4 mS	55.4 mS	49.9 mS

Consent forms

CONSENT FORM

You, Shri./ Smt./ Kum. _____, aged ____ years, S/o / D/o / W/o _____, residing at _____ _____ are requested to be a participant in the research study titled Prevalence of peripheral neuropathy in rheumatoid arthritis ' in Government Medical College Hospital, Coimbatore, conducted by Dr. Hrudya Venugopal, Post Graduate Student in the Department of General Medicine, Coimbatore Medical College. You satisfy eligibility criteria as per the inclusion criteria. You can ask any question or seek any clarifications on the study that you may have before agreeing to participate.

RESEARCH BEING DONE

Prevalence of peripheral neuropathy in rheumatoid arthritis

PURPOSE OF RESEARCH

1. To detect prevalence of peripheral neuropathy in rheumatoid arthritis.
2. To determine the type of neuropathy.
3. To determine association of peripheral neuropathy with age,gender,duration of disease.

PROCEDURES INVOLVED

The research includes Nerve conduction study of patient satisfying ACR criteria,evaluation of Complete Haemogram,LiverFunction Test,RenalFunctionTest,RheumatoidFactor,Erythrocyte Sedimentaion Rate.

DECLINE FROM PARTICIPATION

You are hereby made aware that participation in this study is purely voluntary and honorary and that you have the option and the right to decline from participation in the study.

PRIVACY AND CONFIDENTIALITY

You are hereby assured about your privacy. Privacy of subject will be respected and any information about you or provided by you during the study will be kept strictly confidential.

AUTHORIZATION TO PUBLISH RESULTS

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified; neither will your privacy be breached.

STATEMENT OF CONSENT

I, _____, do hereby volunteer and consent to participate in this study being conducted by Dr. HrudyaVenugopal. I have read and understood the consent form / or it has been read and explained to me. The study has been fully explained to me, and I may ask questions at any time.

Signature / Left Thumb Impression of the Volunteer Date:

Signature and Name of witness Date:

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் மகப்பேறு மற்றும் பெண்கள் மருத்துவ துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவி _____ அவர்கள் மேற்கொள்ளும்

_____

_____

பற்றிய ஆய்வில் செய்முறை மற்றும் அனைத்து விளக்கங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெரிவுபடுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடனும், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னைப் பற்றிய அனைத்து விவரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்வில் இருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் :

தேதி : கையொப்பம் / ரேகை

Master chart

NO	AGE	SEX	ESR	RF	DURATION of RA (YRS)	SENSORY NCN		MOTOR NCN		MIXED NCN		CTS CN	AXONAL	DEMYELINATION	PERIPHERAL NEUROPATHY SYMPTOMS
						UPPER LIMB	LOWER LIMB	UPPER LIMB	LOWER LIMB	UPPER LIMB	LOWER LIMB				
57186	42	F	38	NEGATIVE	7	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
24010	42	F	28	POSITIVE	4	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
26789	35	F	35	POSITIVE	7	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
34587	50	F	30	NEGATIVE	10	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	PRESENT
45634	60	F	29	NEGATIVE	5	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
34876	34	F	28	NEGATIVE	3	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
24556	80	F	32	NEGATIVE	6	PRESENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
45667	41	F	46	NEGATIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	PRESENT
13678	53	F	15	POSITIVE	10	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
25643	67	F	35	POSITIVE	10	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
57843	38	F	30	POSITIVE	15	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
46535	40	F	40	POSITIVE	3	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
45678	69	M	32	POSITIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
54790	60	F	38	POSITIVE	4	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
45789	42	F	28	POSITIVE	2	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
35689	47	M	39	NEGATIVE	15	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
76578	49	F	20	POSITIVE	2	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	PRESENT
57954	50	M	32	POSITIVE	2	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
08534	54	F	33	NEGATIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
07678	56	M	35	POSITIVE	4	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	PRESENT
43268	41	F	34	NEGATIVE	4	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
36557	71	M	30	NEGATIVE	10	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
45690	51	F	34	NEGATIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT

57868	61	M	33	NEGATIVE	6	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
53267	48	F	30	NEGATIVE	8	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
75789	64	F	25	NEGATIVE	4	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT
23456	53	F	38	NEGATIVE	10	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
54466	60	M	40	POSITIVE	2	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
75443	39	F	40	POSITIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
56445	25	F	28	POSITIVE	2	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
54644	20	M	42	NEGATIVE	3	PRESENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
53444	59	F	25	NEGATIVE	5	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	PRESENT
54576	44	F	36	NEGATIVE	2	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
55677	38	F	33	NEGATIVE	4	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
53377	32	F	38	NEGATIVE	6	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
54456	54	F	35	NEGATIVE	3	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
53566	50	F	38	NEGATIVE	5	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
10675	50	F	25	NEGATIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
14067	51	M	32	NEGATIVE	4	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
55736	35	F	37	NEGATIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
53367	33	F	20	POSITIVE	2	PRESENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	ABSENT
53323	48	F	27	POSITIVE	10	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT
56666	57	F	35	NEGATIVE	4	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
71098	55	F	40	POSITIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	PRESENT
57768	48	F	36	NEGATIVE	5	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT
45764	62	M	26	POSITIVE	6	PRESENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
10004	56	M	36	POSITIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	PRESENT	PRESENT	ABSENT	ABSENT
55788	56	F	15	NEGATIVE	4	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT
75779	64	M	25	NEGATIVE	3	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT
23446	53	F	38	NEGATIVE	10	ABSENT	ABSENT	ABSENT	ABSENT	PRESENT	PRESENT	ABSENT	PRESENT	ABSENT	ABSENT